Platelet Aggregation Inhibitors
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	FDA-Approved Indication(s)
aspirin/dipyridamole ER [1]	generic	▪ Risk reduction of stroke in patients who have had transient ischemia of the brain or completed ischemic thrombotic stroke due to thrombosis
aspirin/omeprazole DR (Yosprala®)[2]	generic†, Innovida/Pharmaceutika	▪ For patients who require aspirin for secondary prevention of cardiovascular and cerebrovascular events and who are at risk of developing aspirin-associated gastric ulcers – The aspirin component is indicated for reducing the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli; reducing the combined risk of death and nonfatal myocardial infarction (MI) in patients with a previous MI or unstable angina pectoris; reducing the combined risk of MI and sudden death in patients with chronic stable angina pectoris; and use in patients who have undergone revascularization procedures when there is a pre-existing condition for which aspirin is already indicated. – The omeprazole component is indicated for decreasing the risk of developing aspirin-associated gastric ulcers in patients at risk for developing aspirin-associated gastric ulcers due to age (≥ 55 years) or documented history of gastric ulcers
clopidogrel (Plavix®)[3]	generic, Bristol-Myers Squibb/ Sanofi-Aventis	▪ To reduce MI and stroke in patients with recent MI, recent stroke, or established peripheral artery disease (PAD) ▪ Acute coronary syndrome (ACS): – To reduce MI and stroke in non-ST-segment elevation ACS (unstable angina [UA] or non-ST-elevation myocardial infarction [NSTEMI]) – To reduce MI and stroke in ST-elevation myocardial infarction (STEMI)
dipyridamole[4]	generic	▪ Adjunctive therapy to coumarin anticoagulants in the prevention of postoperative thromboembolic complications of cardiac valve replacement
prasugrel (Effient®)[5]	generic, Eli Lilly/Daiichi Sankyo	▪ Reduction of thrombotic cardiovascular (CV) events (including stent thrombosis) in patients with ACS who are to be managed with percutaneous coronary intervention (PCI) as follows: patients with UA or NSTEMI, or patients with STEMI when managed with either primary or delayed PCI

† Authorized generic.

FDA-Approved Indications (continued)

Drug	Manufacturer	FDA-Approved Indication(s)
ticagrelor (Brilinta®)[6]	AstraZeneca	▪ Reduce risk for CV death, MI, and stroke in patients with ACS or a history of MI (shown to be superior to clopidogrel for at least the first 12 months following ACS); ticagrelor also reduces the rate of stent thrombosis in patients who have been stented for treatment of ACS ▪ Reduce the risk of a first MI or stroke in patients with coronary artery disease (CAD) at high risk for such events (use is not reserved to patients with type 2 diabetes mellitus [T2DM]; however, efficacy was established in this patient population) ▪ Reduce the risk of stroke in patients with acute ischemic stroke (National Institutes of Health [NIH] Stroke Scale score ≤ 5) or high-risk transient ischemic attack (TIA)
vorapaxar (Zontivity®)[7]	Aralez	▪ Reduction of thrombotic CV events in patients with a history of MI or PAD; it has been shown to reduce the rate of the combined endpoint of CV death, MI, stroke, and urgent CV revascularization

Immediate-release aspirin is available over the counter and used for secondary prevention of myocardial infarction (MI), stable and unstable angina (UA), including coronary artery disease (CAD), arterial thromboembolism prophylaxis for patients with prosthetic heart valves in combination with warfarin, secondary prevention of stroke/transient ischemic attack (TIA), and acute treatment of stroke in patients not eligible for thrombolysis.

OVERVIEW

The 2022 Heart Disease and Stroke Statistics update cites cardiovascular (CV) disease as the leading cause of all deaths in the United States (US) in 2019, with coronary heart disease (41.3%) being the leading cause of CV death, followed by stroke (17.2%), among CV deaths.[8] Stroke also causes significant morbidity and mortality in the US and is the fifth leading cause of death behind disease of the heart, cancer, accidents, and chronic lower respiratory disease.[9] Inhibitory effects on platelet aggregation have led to a significant decrease in the rate of vascular events for both primary and secondary CV prevention trials.[10,11] Aspirin has been shown to reduce CV morbidity and mortality in both primary and secondary prevention trials.[12,13,14,15,16]

Studies have identified inter-patient variability of response to the antiplatelet agents. A small percentage of patients with CV disease have aspirin resistance and, therefore, may be at higher risk for CV events.[17] The definition of aspirin resistance is quite variable in the literature and has been described as the failure to prevent a thrombotic event, the inability to inhibit platelet thromboxane formation, or the inability to cause prolongation of bleeding time. Guidelines for the management of aspirin resistance have not been developed. It is unknown if aspirin resistance can be overcome by increasing the dose of aspirin or adding another agent.[18,19,20,21,22,23,24] More high-quality clinical trials evaluating aspirin resistance are needed.

Other antithrombotic drugs have been developed to improve the platelet aggregation inhibition and to improve the safety profile of platelet aggregation inhibitor therapy. Clopidogrel (Plavix), and aspirin/dipyridamole ER are platelet aggregation inhibitors and are useful in the treatment and

prevention of CV and cerebrovascular thrombotic events. Prasugrel (Effient) has shown better efficacy compared to clopidogrel in preventing myocardial infarction (MI) and stent thrombosis in ACS patients undergoing percutaneous coronary intervention (PCI).[25] While long-term safety information is still limited with the use of prasugrel, it has been associated with significantly more major bleeding episodes when compared to clopidogrel-treated patients.[26] Studies have shown ticagrelor (Brilinta) to be favored over clopidogrel in preventing deaths from CV causes, MI, or stroke.[27]

Variability in responsiveness to clopidogrel has also been documented.[28,29,30,31] Inconsistencies in response to clopidogrel may be due to pre-existing variability in platelet response to adenosine diphosphate (ADP), genetic variability (polymorphisms in the hepatic enzymes [e.g., CYP2C19] involved in clopidogrel metabolism, or within the platelet $P2Y_{12}$ receptor), or drug interactions (e.g., proton pump inhibitors).[32,33,34,35,36,37] An association between a CYP2C19 variant and recurrent thrombotic coronary events in patients taking clopidogrel has been reported.[38,39,40,41] Unpredictability in response to thienopyridines has led to the development of point-of-care devices to assess ADP induced platelet aggregation.[42] Currently, recommendations are not in place regarding the use of these devices. In addition, dual aspirin and clopidogrel non-responsiveness has been documented and linked to patients at very high risk of drug-eluting stent thrombosis or death.[43]

The role of the agents included in this review in specific cardiovascular conditions is discussed below.

Primary Prevention of Cardiovascular Disease

The 2016 US Preventative Services Task Force (USPSTF) updated the recommendations for aspirin for the primary prevention of CV disease and colorectal cancer.[44] They recommend low-dose aspirin use in adults aged 50 to 59 years who meet the following requirements: ≥ 10% 10-year CV disease risk, no increased risk of bleed, a life-expectancy of ≥ 10 years, and willingness to take aspirin daily for ≥ 10 years (Grade B). For those aged 60 to 69 years and a 10-year CV disease risk ≥ 10%, the decision to use daily low-dose aspirin should be individualized. Those most likely to benefit are those meeting the criteria described above (Grade C). Data are inconclusive for the benefit of daily low-dose aspirin in patients younger than 50 years and 70 years or older.

The 2012 American College of Chest Physicians (ACCP) evidence-based practice guidelines state that aspirin therapy slightly reduces total mortality, regardless of CV risk profile, if taken over 10 years. In people at moderate to high risk of CV events, the reduction in MI is closely balanced with an increase in major bleeds.[45] For primary prevention in persons aged 50 years or older without symptomatic CV disease, ACCP suggests aspirin low-dose (75 mg to 100 mg daily; Grade 2B). However, FDA guidance from May 2014 states that aspirin should not be used for primary prevention of CV disease or stroke which contradicts the ACCP and USPSTF guidelines.[46]

The 2019 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the primary prevention of cardiovascular disease address this contradiction.[47] These guidelines state that aspirin is well established for secondary prevention of ASCVD and is widely recommended for use in this indication; however, the use of aspirin in primary prevention of ASCVD is more controversial. Furthermore, the use of aspirin for cardiovascular prophylaxis (including, but not limited to, stroke) is reasonable for people whose risk is sufficiently high (> 10-year risk exceeding 10%) for the benefits to outweigh the risks associated with treatment.

Stroke and Transient Ischemia Attack (TIA) Treatment and Prevention

The 2019 AHA/American Stroke Association (ASA) guidelines for the early management of stroke recommend an initial dose of 160 mg to 300 mg of aspirin within 24 to 48 hours after stroke onset (Class I recommendation, Level of Evidence A).[48] Antiplatelet agents should be used to reduce the risk of recurrent stroke rather than oral anticoagulants (Class I recommendation, Level of Evidence A), with the choice of antiplatelet based on patient risk factor profiles, cost, tolerance, relative known efficacy of the agents, and other clinical characteristics (Class I recommendation, Level of Evidence C). Furthermore, dual antiplatelet therapy with aspirin and clopidogrel is recommended to start within 24 hours after a patient presents with minor non-cardioembolic ischemic stroke who did not receive intravenous alteplase and should be continued for 21 days (Class I recommendation, Level of Evidence A). For patients who have a stroke while taking aspirin, increasing the dose of aspirin or switching to an alternative antiplatelet agent for added benefit to prevent a subsequent stroke is not well established (Class IIb recommendation, Level of Evidence B). Secondary stroke prevention using triple antiplatelet therapy with aspirin, clopidogrel, and dipyridamole is harmful and should not be administered (Class III recommendation, Level of Evidence B). The 2021 AHA/ASA guideline for the prevention of stroke in patients with stroke and TIA recommend short-term dual antiplatelet therapy as secondary prevention only in patients with early arriving minor stroke and high-risk TIA or severe symptomatic intracranial stenosis.[49] Long-term dual antiplatelet therapy is not recommended as secondary prevention.

The 2019 AHA/ACC/Heart Rhythm Society (HRS) updated guideline on the management of patients with atrial fibrillation states that patients treated for ACS normally require dual antiplatelet therapy with aspirin plus a platelet $P2Y_{12}$ receptor inhibitor and may require triple therapy with the addition of warfarin or a non-vitamin K oral antagonist for primary prevention for patients with atrial fibrillation at increased risk of stroke.[50] If triple therapy is used, it is recommended to minimize the duration of triple therapy to a period of 4 to 6 weeks (the period with greatest risk for stent thrombosis). Therapy with the use of an oral anticoagulant plus a $P2Y_{12}$ inhibitor (without aspirin) is an option, as well.

AHA/ASA guidelines regarding stroke prevention in women recommend aspirin therapy (75 mg to 325 mg/day) in women with diabetes and women undergoing carotid endarterectomy.[51] Aspirin may also be appropriate for women ≥ 65 years (81 mg/day) to prevent ischemic stroke and myocardial infarction when benefits outweigh the risks of gastrointestinal bleeding and/or hemorrhagic stroke. Clopidogrel is recommended in high-risk patients (e.g., 10-year predicted risk ≥ 10%) intolerant to aspirin.

Acute Coronary Syndrome Treatment and Prevention

In 2014, the American College of Cardiology (ACC) and the AHA released practice guidelines for the management of patients with non-ST-elevation acute coronary syndromes (NSTE-ACS).[52] The majority of patients who present with acute coronary syndrome (ACS) have unstable angina (UA) or non-ST segment elevation myocardial infarction (NSTEMI). Since the presentation of these conditions is similar, the ACC/AHA now refers to both as NSTE-ACS. The 2014 guideline recommends that non-enteric-coated, chewable aspirin (162 mg to 325 mg) should be given to all NSTE-ACS patients without contraindications as soon as possible after presentation, and a maintenance dose of aspirin (81 mg to 325 mg/day) should be continued indefinitely. For NSTE-ACS patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance, a loading dose of clopidogrel is recommended followed by a daily maintenance dose.

Many of the guidelines related to ACS and related procedures (e.g., PCI, coronary artery bypass graft surgery [CABG]) have been published individually. However, in 2016, the ACC/AHA published guidelines specifically regarding dual antiplatelet therapy (DAPT) in various CV conditions.[53] These supersede their recommendations in prior publications while unaddressed ACC/AHA guideline recommendations remain unchanged. In all cases where aspirin is used in DAPT, they continue to recommend 81 mg of aspirin daily as a maintenance dose (range, 75 mg to 100 mg) (Class I). Likewise, they recommend against the use of prasugrel in patients with a prior history of stroke or TIA (Class III). Patients on DAPT undergoing surgery should have aspirin continued, if possible, and the antiplatelet restarted as soon as possible after surgery if it must be discontinued for the surgery (Class I).

For patients with anterior MI and left ventricular (LV) thrombus, or at high risk for LV thrombus who do not undergo stenting, the 2012 ACCP guidelines recommend warfarin plus aspirin (75 mg to 100 mg daily) for the first 3 months (Grade 1B) and DAPT with aspirin plus ticagrelor (Brilinta) or clopidogrel for up to 12 months, as per their ACS recommendation.[54] After 12 months, single antiplatelet therapy with aspirin (75 mg to 100 mg daily) or clopidogrel is recommended as per the ACCP established CAD recommendation. Similar recommendations from the 2016 ACC/AHA DAPT guidelines apply for patients with any ACS who are managed with medical therapy alone and treated with DAPT.[55] Either clopidogrel or ticagrelor is recommended in combination with aspirin, and a duration shorter than 12 months is not recommended.

According to the 2013 American College of Cardiology Foundation (ACCF)/AHA guidelines for the management of patients with STEMI, a loading dose of a $P2Y_{12}$ platelet inhibitor is recommended for STEMI patients for whom PCI is planned in addition to aspirin (162 to 325 mg).[56] The guidelines recommend aspirin 162 to 325 mg before primary PCI (Level of Evidence B, Class I Recommendation); after PCI, aspirin should be continued indefinitely (Level A, Class I). The guidelines also recommend use of prasugrel and ticagrelor as alternatives to clopidogrel. These agents should be given as a loading dose as early as possible to patients with STEMI or at time of PCI. After the placement of a drug-eluting stent (DES) or bare-metal stent (BMS), they recommend DAPT with aspirin indefinitely and a $P2Y_{12}$ platelet inhibitor (clopidogrel, prasugrel, or ticagrelor) for at least 12 months (Class I, Level of Evidence B). This was confirmed in the 2016 DAPT guidelines with the caveat that it is reasonable to use ticagrelor over clopidogrel for maintenance therapy (Class IIa).[57] In STEMI patients with a prior history of stroke and TIA for whom primary PCI is planned, prasugrel is not recommended as part of a dual-antiplatelet therapy regimen (Level of Evidence C).[58] The 2016 ACC/AHA DAPT guidelines state that STEMI patients treated with a fibrinolytic and DAPT should receive at least 14 days of clopidogrel, although 12 months of therapy is preferred (Class I) and a longer duration may be reasonable in select patients (Class IIb).[59]

The 2011 ACCF/AHA/SCAI PCI guidelines state that patients already on aspirin therapy should take 81 mg to 325 mg before PCI (Class I, Level of Evidence B), although guidelines specific for PCI in STEMI patients supersede this recommendation. Patients not on aspirin therapy should be given non-enteric aspirin 325 mg before PCI (Class I, Level of Evidence B).[60,61] After PCI, aspirin should be continued indefinitely (Class I, Level of Evidence A), and aspirin 81 mg daily is preferred to higher aspirin maintenance doses (Class IIa, Level B).[62] $P2Y_{12}$ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) should be continued for at least 12 months in NSTE-ACS post-PCI patients treated with coronary stents (Class I), which was also confirmed in the 2016 DAPT recommendations for both STEMI and NSTE-ACS post-PCI.[63] Early discontinuation of DAPT greatly increases the risk of stent thrombosis, MI, and death,

and poor adherence in post-DES patients within the first 30 days of therapy and has been shown to reduce the beneficial effects on mortality.[64,65] Specifically, the 2016 DAPT recommendations further state that in patients with ACS (STEMI or NSTE-ACS) treated with DAPT, it is reasonable to use ticagrelor over clopidogrel for maintenance therapy (Class IIa).[66] Likewise, in those without a high bleeding risk and without a history of stroke or TIA, it is reasonable to choose prasugrel over clopidogrel (IIa). Longer use may be reasonable in select patients who have tolerated DAPT therapy (Class IIb), and 6 months of therapy may be reasonable in those with DES and a high bleed risk (Class IIb).

Clopidogrel, with the addition of aspirin, is efficacious in reducing major cardiac adverse events following successful coronary stent implantation.[67,68,69,70] The 2014 ACC/AHA NSTE-ACS guidelines and the 2013 ACCF/AHA STEMI guidelines state the duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor should be minimized as much as possible in order to limit the risk of bleeding. Additionally, both guidelines suggest lowering the therapeutic INR range to 2 to 2.5 for NSTE-ACS patients treated with triple antithrombotic therapy (Class IIb).[71,72]

The 2012 ACCP evidence-based clinical practice guidelines recommend the combination of aspirin and ticagrelor, clopidogrel, or prasugrel for up to 12 months in patients who undergo stent placement following ACS (Grade 1B) with a preference of aspirin plus ticagrelor over aspirin plus clopidogrel (Grade 2B).[73] For patients undergoing elective PCI but no stenting, ACCP suggests aspirin 75 mg to 325 mg daily and clopidogrel for the first year and single antiplatelet therapy after 12 months (Grade 1A [month 1]; Grade 2C [months 2-12]; Grade 1B [> 1 year]). For secondary prevention in patients with established CAD, defined as 1-year post-ACS, with prior revascularization, coronary stenosis > 50%, and/or evidence for cardiac ischemia, ACCP recommends long-term, low-dose aspirin or clopidogrel (Grade 1A).

The 2011 ACCF/AHA CABG guidelines state that, for elective CABG, clopidogrel and ticagrelor should be discontinued for at least 5 days before surgery (Class I, Level B) and prasugrel for at least 7 days before surgery (Class I, Level C).[74] In urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding complications (Class I, Level B). The 2016 DAPT guidelines state that in patients with ACS undergoing CABG and treated with DAPT, the $P2Y_{12}$ platelet inhibitor should be resumed postoperatively to complete 12 months of treatment (Class I).[75] The 2012 ACCP guidelines suggest that, in patients who are receiving dual antiplatelet drug therapy and require CABG surgery, aspirin should be continued around the time of surgery and clopidogrel/prasugrel should be interrupted 5 days before surgery (Grade 2C).[76]

The 2016 AHA/ACC DAPT guidelines also weighed in on the role of DAPT in patients with stable ischemic heart disease (SIHD).[77] In stented SIHD patients treated with DAPT, they state clopidogrel should be used for at least 1 month in those with a BMS and for at least 6 months in those with a DES (Class I). Longer use may be reasonable in select patients who have tolerated DAPT therapy (Class IIb). Likewise, 3 months of therapy may be reasonable in those with a DES and a high bleed risk (Class IIb). In patients undergoing CABG following stent implantation treated with DAPT, the antiplatelet should be resumed postoperatively until the recommended duration of therapy is completed (Class I). It also is reasonable to use DAPT for 12 months to improve vein graft patency in this population (Class IIb) and to continue DAPT in SIHD patients treated for an MI 1 to 3 years earlier if the therapy has been tolerated (Class IIb). DAPT therapy is not beneficial in SIHD patients without a history of ACS, stent implantation, or recent (< 12 months) CABG.

Peripheral Arterial Disease (PAD)

The 2016 AHA/ACC guidelines state that aspirin alone 75 mg to 325 mg per day or clopidogrel alone (75 mg per day) is recommended to reduce the risk of MI, stroke, and vascular death in patients with symptomatic PAD (Class I, Level of Evidence B).[78] Data on the effectiveness of DAPT in PAD with both aspirin and clopidogrel are limited, but it may be considered in select high-risk patients. The addition of vorapaxar to existing antiplatelet therapy in symptomatic patients is uncertain.

For the primary prevention of CV events in patients with asymptomatic PAD, the 2012 ACCP guidelines suggest aspirin 75 mg to 100 mg daily (Grade 2B).[79] However, the FDA's guidance from May 2014 discussed above states that aspirin should not be used for primary prevention of CV disease or stroke, which contradicts the ACCP's earlier guidance.[80] For secondary prevention in those with symptomatic PAD, ACCP recommends aspirin 75 mg to 100 mg daily or clopidogrel (Grade 1A). In patients with symptomatic carotid stenosis, ACCP recommends clopidogrel, aspirin/dipyridamole extended-release, or aspirin (75 mg to 100 mg daily) (Grade 1A), with preference to either clopidogrel or aspirin/dipyridamole extended-release over aspirin (Grade 2B).

PHARMACOLOGY[81,82,83,84,85,86,87,88,89]

Aspirin irreversibly inhibits platelet cyclooxygenase and, thus, inhibits the generation of thromboxane A2, a powerful inducer of platelet aggregation and vasoconstriction. Yosprala contains omeprazole in addition to aspirin to reduce the risk of aspirin-associated gastric ulcers. Omeprazole, a proton pump inhibitor (PPI), blocks the final step of gastric acid production.

Dipyridamole increases intraplatelet cyclic-3',5'-adenosine monophosphate (cAMP) levels, a platelet inhibitor, by inhibiting cAMP degradation and uptake of adenosine into platelets, endothelial cells, and erythrocytes. Dipyridamole presumably inhibits adenosine deaminase, as well as phosphodiesterase, allowing levels of cAMP to remain increased.

Aspirin/dipyridamole ER provides 2 mechanisms of anti-aggregation effects on platelets by administration of aspirin and dipyridamole together.

Clopidogrel (Plavix) is metabolized by CYP450 enzymes to its active metabolite that selectively inhibits the binding of adenosine diphosphate (ADP) to platelet $P2Y_{12}$ receptors and the subsequent ADP-mediated activation of the glycoprotein IIb/IIIa complex. Activation of this complex leads to irreversible inhibition of platelet aggregation.

Prasugrel (Effient), a thienopyridine $P2Y_{12}$ platelet inhibitor, is converted to an active metabolite by CYP3A4 and CYP2B6, which inhibits platelet action by irreversibly binding to the platelet ADP receptor.

Ticagrelor (Brilinta), a cyclopentyltriazolopyrimidine $P2Y_{12}$ platelet inhibitor, and its major metabolite reversibly inhibit the platelet $P2Y_{12}$ ADP-receptor and thereby prevent signal transduction and platelet activation and aggregation.

Vorapaxar (Zontivity), a reversible antagonist of the protease-activated receptor-1 (PAR-1), inhibits thrombin-induced and thrombin receptor agonist peptide (TRAP)-induced platelet aggregation.

PHARMACOKINETICS[90,91,92,93,94,95,96,97]

Drug	Half-Life (hr)	Metabolites	Excretion (%)
aspirin (immediate release)*	0.33	metabolites	Renal: pH dependent Feces: varies
clopidogrel (Plavix)	6 – parent drug 8 – inactive metabolite	carboxylic acid derivative is inactive; parent is inactive	Renal: 50 Feces: 46
dipyridamole	13.6	monoglucuronide metabolite (low activity)	Renal: < 5 Feces: 95
dipyridamole	10	inactive glucuronide metabolite	Predominately feces
omeprazole (Yosprala)	1	hydroxyomeprazole (major) and other metabolites; minimal activity	Renal: 77 Feces: 23
prasugrel (Effient)	7 (2 to 15) – active metabolite	active and inactive metabolites	Renal: 68 Feces: 27
ticagrelor (Brilinta)	7 – parent drug 9 – active metabolite	active metabolite	Renal: 26 Feces: 58
vorapaxar (Zontivity)	3 to 4 days	active metabolites	Renal: 25 Feces: 58

The half-life of the aspirin component of Yosprala is 2.4 hours.

The pharmacokinetics of the individual agents of aspirin/dipyridamole ER are not affected by co-administration.

Clopidogrel is converted to its active form by the CYP2C19 enzyme. Clopidogrel active metabolite pharmacokinetics and antiplatelet effects differ according to CYP2C19 genotype. Patients with a CYP2C19 variant may be poor metabolizers of the drug and do not effectively convert clopidogrel to its active form, making clopidogrel less effect on platelets and less able to prevent MI, stroke, and CV death. The prevalence of CYP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differs according to race. Published frequencies for poor CYP2C19 metabolizer genotypes are approximately 2% for Caucasians, 2% for African Americans, and 14% for Chinese.[98] The *CYP2C19*2* and *CYP2C19*3* alleles account for 85% of reduced function alleles in Caucasians and 99% in Asians. The impact of CYP2C19 genotype on the pharmacokinetics of clopidogrel's active metabolite has been evaluated in several studies. Reduced CYP2C19 metabolism in intermediate and poor metabolizers decreased the maximum concentration (Cmax) and exposure (area under the curve [AUC]) of the active metabolite by 30% to 50% following 300 or 600 mg loading doses and 75 mg maintenance doses. The association between CYP2C19 genotype and clopidogrel treatment outcome was evaluated in *post-hoc* analyses and several cohort studies.[99,100,101,102,103,104,105] The results ranged from increased CV events in impaired metabolizers to no CV event rate difference in various genotypes. In addition, paraoxonase-1 (PON1) has been recently identified as a new enzyme for clopidogrel bioactivation, with the *Q19R* polymorphism determining both the rate of active metabolite and clopidogrel clinical activity.[106]

In March 2010, the FDA added a boxed warning to the label for clopidogrel regarding patients that are poor metabolizers of clopidogrel who may not receive the full benefits of the drug and issued a statement the following October.[107] The warning informs healthcare professionals of the availability of tests to identify genetic differences in CYP2C19 function and advises consideration of alternative

antiplatelet medications or alternative dosing strategies for clopidogrel in patients identified as poor metabolizers. The FDA emphasized additional facts that may be a source of confusion among healthcare professionals: (1) with regard to the PPI drug class, this recommendation applies only to omeprazole and not to all PPIs as not all PPIs have the same inhibitory effect on the CYP2C19 enzyme that is crucial for conversion of clopidogrel into its active form; and (2) pantoprazole (Protonix) may be an alternative PPI for consideration since it is a weak inhibitor of CYP2C19 and has less effect on the pharmacological activity of clopidogrel than omeprazole. However, since this statement release, the clopidogrel label recommends against concomitant use of clopidogrel with omeprazole or esomeprazole.

In response to this warning, ACCF/AHA recommends that genetic testing may be considered before starting clopidogrel therapy in patients believed to be at moderate or high risk for poor outcomes (e.g., patients undergoing elective high-risk PCI procedures).[108,109] If such testing identifies a potential poor metabolizer, other therapies, particularly prasugrel (Effient) for coronary patients, should be considered. Higher loading doses (600 mg versus 300 mg), double-dose loading (600 mg twice over 2 hours), and higher maintenance doses of clopidogrel (150 mg daily) have been found to improve platelet inhibition and might be considered alternatives for high-risk patients who respond poorly to standard dosages of clopidogrel, although there is uncertainty of the long-term safety and efficacy of this approach. In November 2010, the ACCF/American College of Gastroenterology (ACG)/AHA updated their expert consensus document regarding gastrointestinal (GI) risk of antiplatelet agents and nonsteroidal anti-inflammatory drugs (NSAID).[110] It states that clopidogrel alone, aspirin alone, and their combination are all associated with increased risk of GI bleeding and patients most at risk are those with prior GI bleeding; advanced age; concurrent use of anticoagulants, steroids, or NSAIDs, including aspirin; and *Helicobacter pylori* infection. This statement does not recommend routine use of PPIs in patients on antiplatelet therapy, but advises that PPIs are appropriate to reduce GI bleeding among patients with multiple risk factors for GI bleeding who require antiplatelet therapy. Clinical decisions regarding concomitant use of PPIs and thienopyridines must balance overall risks and benefits, considering both CV and GI complications. Likewise, according to the 2016 ACC/AHA focused update on dual antiplatelet therapy, PPIs should be used in patients with a history of prior GI bleeding who are on DAPT therapy (Class I); however, routine use of PPI's in those at low risk for GI bleeding is not recommended (Class III).[111]

Prasugrel (Effient) is a prodrug that requires hepatic conversion via CYP3A4 and CYP2B6 (with lesser involvement of CYP2C9 and CYP2C19) to its active metabolite. Prasugrel and ticagrelor (Brilinta) are not significantly affected by genetic variations that reduce CYP2C19 enzymes and, therefore, are not expected to be affected by pharmacogenomics or CYP2C19 inhibitors (e.g., omeprazole). Ticagrelor and its major active metabolite are weak P-glycoprotein (P-gp) substrates and inhibitors. The major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite is CYP3A4.

CONTRAINDICATIONS/WARNINGS[112,113,114,115,116,117,118]

Clopidogrel (Plavix), prasugrel (Effient), ticagrelor (Brilinta), and vorapaxar (Zontivity) are contraindicated in patients with active pathological bleeding, such as bleeding peptic ulcer or intracranial hemorrhage (ICH).

Prasugrel and vorapaxar are contraindicated in patients with prior TIA or stroke.

Clopidogrel, prasugrel, and ticagrelor are contraindicated in patients with hypersensitivity to their active ingredient or any of the excipients. Cross-reactivity among thienopyridines may occur. Aspirin/dipyridamole ER and aspirin/omeprazole DR (Yosprala) are contraindicated in patients with hypersensitivity to their respective active components or any excipients. Aspirin/dipyridamole ER, and aspirin/omeprazole DR should not be administered to patients with known allergy to NSAIDs or to patients with the syndrome of asthma, rhinitis, and nasal polyps. Aspirin and aspirin-containing products should not be given to children or teenagers with viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of aspirin in certain viral illnesses. Aspirin/omeprazole DR is also contraindicated in patients receiving rilpivirine-containing products.

Aspirin-containing products have several warnings in their labeling. Patients who consume 3 or more alcoholic drinks every day should be counseled about the bleeding risks involved with chronic heavy alcohol use while taking aspirin. Due to the aspirin component, the increase in bleeding time may adversely affect patients with inherited or acquired (liver disease or vitamin K deficiency) bleeding disorders. Aspirin has known gastrointestinal (GI) adverse effects that include stomach pain, heartburn, nausea, vomiting, and GI bleeding. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, it is important to monitor for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Patients with a history of active peptic ulcer disease should avoid using aspirin (immediate or extended-release) due to the potential for gastric mucosal irritation and bleeding. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has also been reported in patients taking aspirin.

Aspirin products may cause fetal harm when administered to pregnant women and should be avoided during the third trimester due to the risk of premature closure of the ductus arteriosus. Additionally, aspirin/dipyridamole (Yosprala) labeling warns the use of NSAIDs, at 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios or neonatal renal impairment.

Aspirin/omeprazole DR warrants additional warnings related to its omeprazole component, a PPI. Some of these are related to drug interactions (e.g., clopidogrel, strong CYP 3A4 inducers, methotrexate), which are described in more detail below. Other warnings related to the omeprazole component include masking of gastric malignancy symptoms (resolution of symptoms during omeprazole use does not indicate lack of malignancy), acute tubulointerstitial nephritis (TIN), *Clostridium difficile*-associated diarrhea (CDAD), cutaneous and systemic lupus erythematosus, bone fracture with long-term use, cyanocobalamin deficiency, hypomagnesemia, and interactions with select diagnostic tests for neuroendocrine tumors. In reported case series, some patients were diagnosed on biopsy and in the absence of extra-renal manifestations (e.g., fever, rash, or arthralgia). Patients with TIN may experience a range of symptoms (symptomatic hypersensitivity to non-specific reduced renal function [malaise, nausea, anorexia]). PPIs have been associated with the development of fundic gland polyps, and the risk increases with long-term use. When possible, the shortest duration of PPI treatment should be used for the condition being treated.

Oral dipyridamole and aspirin/dipyridamole therapy can lead to an increased risk for cardiovascular side effects and impaired stress test sensitivity in patients who receive stress testing with intravenous dipyridamole and other adrenergic agents. Treatment with dipyridamole should be stopped 48 hours prior to testing to mitigate these risks.

Clopidogrel has a boxed warning stating its effectiveness depends on adequate metabolism to the active metabolite. Tests are available to identify poor metabolizers. An alternative $P2Y_{12}$ inhibitor

should be used in patients who are poor CYP2C19 metabolizers. Additionally, concomitant use of drugs that induce CYP2C19 would be expected to result in increased drug levels of the active metabolite of clopidogrel and may increase the risk for bleeding; therefore, concomitant use of strong CYP2C19 inducers should be avoided with clopidogrel.

Clopidogrel has been rarely associated with TTP. Onset of TTP is generally within the first 2 weeks of therapy.[119] Premature discontinuation may increase the risk of CV events. Likewise, clopidogrel increases the risk of bleeding. Clopidogrel should be discontinued 5 days prior to elective surgery with a major risk of bleeding and should be restarted as soon as possible. Clopidogrel impairs angiogenesis, a process critical for repair of GI mucosal disruptions, potentially leading to bleeding. Combining a PPI that inhibits CYP2C19 (e.g., omeprazole, esomeprazole) may reduce clopidogrel's efficacy. Concurrent use should be avoided.

In 2014, the FDA issued a safety announcement regarding preliminary data from a clinical trial showing that treatment for 30 months with dual antiplatelet therapy (aspirin plus either clopidogrel or prasugrel) decreased the risk of myocardial infarction and clot formation in stents, but there was an increased overall risk of death compared to 12 months of treatment.[120] However, after review, the FDA issued a drug safety communication stating that clopidogrel does not increase or decrease overall risk of death in patients with, or at risk for, heart disease or risk of cancer or death from cancer (prasugrel not addressed).[121]

Warnings associated with prasugrel include increased risk of bleeding (boxed warning; particularly CABG bleeding) and increased risk of stent thrombosis, MI, and death when prasugrel is discontinued prematurely. Prasugrel should not be started if CABG is anticipated, and it should be discontinued at least 7 days prior to any surgery. Other bleeding risk factors include weight < 60 kg, propensity for bleeding, or use of other medications that increase bleeding risk. Prasugrel is generally not recommended in patients who are ≥ 75 years old due to increased risk of fatal and intracranial bleeding and uncertain benefit except in high-risk patients who are ≥ 75 years (e.g., with prior MI, diabetes). TTP has been reported with the use of prasugrel, sometimes with brief exposures of < 2 weeks.

Ticagrelor has boxed warnings regarding potential for significant, sometimes fatal, bleeding; recommendation against use in patients planned to undergo urgent CABG, when possible discontinue at least 5 days prior to any surgery. Bleeding should be a suspected cause in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures when ticagrelor is used, and bleeding should be managed without discontinuing ticagrelor whenever possible, since stopping the drug when used for CAD may increase the risk of subsequent CV events (MI, stroke, death); if ticagrelor must be temporarily discontinued for surgery with major bleeding risk, stop for 5 days before surgery and restart as soon as hemostasis has occurred. After an initial dose used for ACS, with the maintenance dose of aspirin is 75 mg to 100 mg per day; however, maintenance doses of aspirin above 100 mg reduce the effectiveness of ticagrelor and should be avoided. Patients treated for acute ischemic stroke or TIA with a NIH stroke score > 5 as well as patients receiving thrombolysis are not recommended to receive ticagrelor. Ticagrelor carries a warning and should be avoided in patients with severe hepatic impairment, which may increase drug exposure. Dyspnea has been reported in clinical trials with ticagrelor and was generally mild to moderate in severity and self-limiting. No specific therapy is required for dyspnea due to ticagrelor, and ticagrelor should be continued if possible; however, if dyspnea is intolerable and ticagrelor is

discontinued, consider another antiplatelet therapy. Ticagrelor has been associated with central sleep apnea (CSA) including Cheyne-Stokes respiration (CSR) in the post-marketing setting, including recurrence or worsening of CSA/CSR following rechallenge. If CSA is suspected in patients taking ticagrelor, patients should be considered for further evaluation. Ticagrelor also carries a warning regarding bradyarrhythmia as it may cause ventricular pauses, including AV block. Patients with a history of sick sinus syndrome, second- or third-degree AV block, or bradycardia-related syncope without a pacemaker were excluded from key clinical trials and may be at a greater risk for bradyarrhythmia. Ticagrelor carries a warning regarding false negative results in platelet functional tests including the heparin-induced platelet aggregation (HIPA) assay, among others. Providers who are interpreting tests for heparin-induced thrombocytopenia (HIT) using this assay should be informed of patients taking ticagrelor.

Vorapaxar also increases the risk of bleeding, including ICH and fatal bleeding, in proportion to the patient's underlying bleeding risk. General risk factors for bleeding include older age, low body weight, reduced renal or hepatic function, history of bleeding disorders, and use of certain concomitant medications that increase the risk of bleeding. Avoid concomitant use of warfarin or other anticoagulants. Significant inhibition of platelet aggregation remains 4 weeks after discontinuation. Therefore, withholding vorapaxar for a brief period will not be useful in managing an acute bleeding event because of its long half-life; there is no known treatment to reverse the antiplatelet effect of vorapaxar.

Risk Evaluation and Mitigation Strategy (REMS)[122]

Clopidogrel, ticagrelor, and prasugrel previously had REMS requirements, but they have subsequently been removed.

DRUG INTERACTIONS[123,124,125,126,127,128,129,130]

Drug	warfarin	NSAIDs	Comment
aspirin/dipyridamole ER	May be at higher risk for bleeding	May be at higher risk for bleeding	Dipyridamole may increase the CV effects of adenosine
aspirin/omeprazole DR (Yosprala)	May be at higher risk for bleeding	May be at higher risk for serious adverse effects, including bleeding and renal impairment	-
clopidogrel (Plavix)	May be at higher risk for bleeding	May increase risk of GI bleeding	-
dipyridamole	-	-	Dipyridamole may increase the CV effects of adenosine
Prasugrel (Effient)	May be at higher risk for bleeding	May increase the risk of bleeding	Can be administered with drugs that are inducers or inhibitors of cytochrome P450 enzymes
ticagrelor (Brilinta)	May be at higher risk for bleeding	May be at higher risk for bleeding	Use with aspirin maintenance doses above 100 mg reduced the effectiveness of ticagrelor
Vorapaxar (Zontivity)	May be at higher risk for bleeding	May be at higher risk for bleeding	Avoid concomitant use with warfarin

When combined with inhibitors of the renin-angiotensin system, aspirin may result in deterioration of renal function, which is usually reversible, in patients who are elderly, volume-depleted, or have impaired renal function. Aspirin may displace protein-bound agents, such as phenytoin and valproic acid and may also inhibit the renal clearance of methotrexate.

The omeprazole component of aspirin/omeprazole DR (Yosprala) may impact drugs that require an acidic gastric environment for adequate absorption (e.g., select antiviral drugs, iron salts, mycophenolate, erlotinib, dasatinib, nilotinib). Omeprazole may also interact with the following drugs: methotrexate (increased methotrexate exposure), CYP2C19 substrates (e.g., clopidogrel, citalopram), digoxin (increased digoxin exposure), and tacrolimus (increased tacrolimus exposure). Likewise, doses of aspirin > 100 mg are not recommended with ticagrelor as higher doses may reduce ticagrelor's efficacy as mentioned above.

Clopidogrel is a prodrug which requires hepatic conversion in part via CYP2C19 to its active metabolite.[131,132] As described above, select PPIs (e.g., omeprazole, esomeprazole) may impair clopidogrel's efficacy due to decreased conversion to its active metabolite. [133,134,135,136,137,138,139,140] When concomitant administration of a PPI is required, another acid-reducing agent with minimal or no CYP2C19 inhibitory effect on the formation of clopidogrel active metabolite is recommended. In clinical trials, omeprazole reduced the antiplatelet activity of clopidogrel when given concomitantly or 12 hours apart. A similar reduction in antiplatelet activity was observed with esomeprazole when given concurrently with clopidogrel. Dexlansoprazole (Dexilant), lansoprazole (Prevacid), and pantoprazole (Protonix) had less effect on the antiplatelet activity of clopidogrel than omeprazole or esomeprazole. Drugs that induce CYP2C19 (e.g., rifampin) may result in increased drug levels of the active metabolite of clopidogrel and, therefore, increased platelet inhibition, which may increase the risk of bleeding. Due to this interaction, concomitant use of strong CYP2C19 inducers with clopidogrel should be avoided.

Clopidogrel may increase the systemic exposure of drugs that are CYP2C8 substrates (e.g., repaglinide) as it is an inhibitor of this hepatic enzyme. When clopidogrel is used concomitantly with repaglinide, the initial dose of repaglinide is 0.5 mg with each meal with dose titration based on blood glucose levels (maximum, 4 mg/day). If the patient is already stabilized on doses > 4 mg/day, decrease the dose based on blood glucose levels to ≤ 4 mg/day).

Coadministration of certain platelet aggregation inhibitors, such as clopidogrel, ticagrelor, and prasugrel, with opioid agonists may delay and reduce the absorption of the platelet aggregation inhibitor and its active metabolite. This is presumably due to slowed gastric emptying. Consider the use of a parenteral anti-platelet agent in acute coronary syndrome in patients requiring coadministration of morphine or other opioid agonists.

Avoid ticagrelor use with strong inhibitors of CYP3A (e.g., ketoconazole, clarithromycin, ritonavir) or potent inducers of CYP3A (e.g., rifampin, phenytoin, carbamazepine). Ticagrelor inhibits the P-glycoprotein (P-gp) transporter; therefore, digoxin levels should be monitored with initiation of, or change in, ticagrelor therapy. Avoid simvastatin and lovastatin doses above 40 mg as coadministration may result in increased exposure.

Concomitant use of vorapaxar with strong inhibitors CYP3A (e.g., ketoconazole, clarithromycin, ritonavir) or strong inducers of CYP3A (e.g., rifampin, phenytoin, carbamazepine) should be avoided.

ADVERSE EFFECTS[141,142,143,144,145,146,147,148]

Drug	Dyspepsia	Nausea	Rash	Dizziness	Headache	Diarrhea	Discontinuation Rate	Hemorrhage
placebo n=1,649 ESPS2 data	16.7	14.1	nr	nr	32.9	9.8	21	1.5
aspirin 25mg twice daily n=1,649	18.1	12.7	nr	nr	33.8	6.8	19	2.8
aspirin 325 mg daily n=9,586 CAPRIE data	6.1	3.8	3.5	6.7	7.2	3.4	13	2.7
aspirin/ dipyridamole ER n=1,650	18.4	16	nr	nr	39.2	12.7	25	3.3 (type not specified)
aspirin/ omeprazole DR (Yosprala) n=521	reported	3	reported	reported	reported	3	7	reported
clopidogrel (Plavix)[149] n=9,599	5.2	3.4	4.2	6.2	7.6	4.5	13	2 (GI)
clopidogrel (Plavix) (n=9,186) PLATO data	nr	3.8	nr	3.9	5.8	3.3	5.4	11.2
clopidogrel (Plavix) + aspirin n=6,716 TRITON-TIMI 38 data	nr	4.3	2.4	4.6	5.3	2.6	6.3	1.7 (p=0.029)
dipyridamole ER 200 mg twice daily n=1,654	17.4	15.4	nr	nr	38.3	15.5	25	1.5
dipyridamole n=147	reported	reported	2.3 (1.1)	13.6 (8.2)	2.3 (0)	reported	nr	reported with concurrent warfarin
prasugrel (Effient) + aspirin n=6,741	nr	4.6	2.8	4.1	5.5	2.3	7.2	major bleeding non-CABG related 2.2

Adverse effects are indicated as percentage occurrence. Adverse effects data are compiled from package inserts and cannot be considered comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported

Adverse Effects (continued)

Drug	Dyspepsia	Nausea	Rash	Dizziness	Headache	Diarrhea	Discontinuation Rate	Hemorrhage
ticagrelor (Brilinta)[150] (n=9,235)	nr	4.3	nr*	4.5	6.5	3.7	7.4	major bleed 11.6
ticagrelor (Brilinta) + aspirin[151] n=9,619	nr	nr	nr	nr	nr	nr	due to bleeding 4.9 (1.3)	major bleed 2.2 (1)
ticagrelor (Brilinta) + aspirin[152] n=5,523	nr	nr	nr	nr	nr	nr	due to bleeding 2.8 (0.6)	severe bleed 0.5 (0.1)
vorapaxar (Zontivity) n=10,059	nr	nr	nr	nr	nr	nr	nr	severe 1 (0.8) moderate-severe 3 (2) GUSTO bleeding (mild-severe) 25 (17.6)

Adverse effects are indicated as percentage occurrence. Adverse effects data are compiled from package inserts and cannot be considered comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported

*Has been reported in post marketing experience.

Within the fatal bleeding category in the PLATO study, the rate of fatal non-intracranial bleeding was greater in the clopidogrel group (n=21 [0.3%] than the ticagrelor group (n=9 [0.1%]); p=0.03) while a greater number of fatal intracranial bleeds occurred in the ticagrelor group (n=11 [0.1%]) versus the clopidogrel group (n=1 [0.01%]); p=0.02). Ticagrelor was associated with a higher rate of PLATO-defined non-CABG major bleeding than clopidogrel (4.5% versus 3.8%, respectively; p=0.03). The most common non-hemorrhagic adverse event that occurred when comparing ticagrelor and clopidogrel was dyspnea which was reported in 13.8 and 7.8% of patients, respectively.[153] Also, in a Holter sub study of about 3,000 patients in the PLATO study, more patients had ventricular pauses with ticagrelor then with clopidogrel (6% versus 3.5%, respectively, in the acute phase; and 2.2% versus 1.6%, respectively after 1 month). Laboratory test changes in the PLATO study included greater increases in serum uric acid levels and creatinine levels in the ticagrelor group compared to the clopidogrel group. In the THEMIS study conducted in patients with CAD and T2DM who had not had a first CV event, there were 3 intracranial hemorrhages with ticagrelor compared to 2 with placebo, and fatal bleeds occurred in 1 ticagrelor-treated patient compared with no placebo patients. In the THALES study conducted in patients with a mild-to-moderate acute noncardioembolic ischemic stroke or TIA, there were 21 intracranial hemorrhages with ticagrelor compared to 6 with placebo, and fatal bleeds were almost all intracranial hemorrhages (11 ticagrelor-treated patients versus 2 placebo [aspirin only] patients).

The most common adverse effect that occurred when comparing vorapaxar to placebo was bleeding. Twenty-five percent of patients in the vorapaxar group experienced any GUSTO bleeding (mild-severe) compared to 17.6% in the placebo group. Other adverse reactions that occurred at a rate of at least 2% and at least 10% greater than placebo were anemia (5%), depression (2.4%), and rashes, eruptions, and exanthemas (2.2%).

A meta-analysis evaluated the risk of bleeding complications associated with antiplatelet agents in 51 randomized trials with 338,191 patients.[154] Low-dose aspirin (< 100 mg daily) and dipyridamole have the lowest risk of bleeding (3.6% and 6.7%, respectively). Aspirin doses exceeding 100 mg daily had a similar risk for bleeding as clopidogrel. A systematic review of 22 clinical trials evaluated the adverse events with aspirin (75 mg to 325 mg daily) and clopidogrel associated with therapy for primary or secondary prophylaxis for CV events.[155] Aspirin was associated with an increased risk of major bleeding, major GI bleeding, and intracranial bleeding compared to placebo. The increased risk with low-dose aspirin was 1.7- to 2.1-fold; however, the absolute increased risk was only a 0.13% per year. A dose-related effect was not observed when dividing the aspirin doses into 2 groups of 75 mg to 162.5 mg daily doses versus 162.5 mg to 325 mg daily doses in the analysis, which conflicts with other available data. Of the studies included, clopidogrel was not compared to placebo. One study included in the analysis had increased major GI bleeding with aspirin 325 mg compared to clopidogrel (relative risk [RR], 1.45; 95% confidence interval [CI], 1 to 2.1) with an absolute increase in risk of 0.12% per year associated with aspirin use (95% CI, 0 to 0.28).

SPECIAL POPULATIONS[156,157,158,159,160,161,162]

Pediatrics

Safety and effectiveness have not been established for aspirin/omeprazole DR (Yosprala), clopidogrel (Plavix), prasugrel (Effient), ticagrelor (Brilinta), vorapaxar (Zontivity), or aspirin/dipyridamole ER in pediatric patients. Safety and effectiveness of dipyridamole in patients below the age of 12 years have not been established. The use of aspirin in children should be avoided due to the risk of Reye's syndrome with aspirin usage in certain viral illnesses.

The 2012 ACCP evidence-based clinical guidelines state that aspirin remains the most common antiplatelet agent used in pediatrics.[163] The dose of aspirin for optimal inhibition of platelet aggregation is not known, although empiric low doses of 1 to 5 mg/kg/day have been suggested (Grade 2C). Dipyridamole has also been used in pediatrics, as a second-line antiplatelet agent or in combination with aspirin therapy. Dipyridamole doses of 2 to 5 mg/kg per day are used. Little in the literature is available on the use of dipyridamole in pediatrics.

Pregnancy

Previously prasugrel was assigned Pregnancy Category B; however, its labeling was updated for compliance with the Pregnancy and Lactation Labeling Rule (PLLR). There are no data with prasugrel use in pregnant women to inform a drug-associated risk; conduct a risk versus benefit assessment when prescribing prasugrel to a pregnant woman.

Previously clopidogrel was assigned Pregnancy Category B. Clopidogrel labeling has now been updated for compliance with the PLLR. Current published literature and data from postmarketing surveillance

with clopidogrel use in pregnant women have not identified any drug-associated risks for major birth defects or miscarriage.

Previously, ticagrelor was assigned Pregnancy Category C. Ticagrelor labeling has now been updated for compliance with the PLLR. Available data from case reports with ticagrelor use in pregnant women have not identified any drug-associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Aspirin should not be used within 1 week preceding or during labor and delivery, as the risk of hemorrhage is increased. Due to the risk of low birth weight, increased incidence for intracranial hemorrhage in premature infants, stillbirths, and neonatal death, and aspirin/dipyridamole ER should be avoided in the third trimester of pregnancy. Aspirin may lead to premature closure of the fetal ductus arteriosus.

Aspirin/omeprazole DR has not been assigned a category based on the PLLR. Information regarding the aspirin component is described above. Data with omeprazole have not reported a clear association with major birth defects or miscarriage risk.

Previously aspirin/dipyridamole ER was assigned Pregnancy Category D. Aspirin/dipyridamole ER labeling has now been updated for compliance with the PLLR. Current published literature and postmarketing experience with aspirin/dipyridamole ER use in pregnant women have not identified any drug-associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Previously vorapaxar was assigned Pregnancy Category B. Vorapaxar labeling has now been updated in compliance with the PLLR. A potential for serious adverse reactions (e.g., maternal bleeding/hemorrhage) exists in pregnant women who take vorapaxar, and the long half-life of the drug renders it essentially irreversible. Discontinue vorapaxar in women who become pregnant once the pregnancy is detected and initiate an alternative agent with a shorter duration of action. Available data from postmarketing experience with vorapaxar use in pregnant women are insufficient to evaluate for a drug-associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Renal Impairment

Aspirin-containing products should be avoided in severe renal failure. No dosage adjustment is recommended for clopidogrel, dipyridamole, prasugrel, ticagrelor, or vorapaxar in renal impairment.

Hepatic Impairment

Aspirin-containing products should be avoided in severe hepatic insufficiency. Likewise, omeprazole exposure increases in hepatic impairment; thus, aspirin/omeprazole DR should be avoided in patients with any degree of hepatic impairment. No dosage adjustment is needed for clopidogrel in hepatic impairment. Elevations of hepatic enzymes and hepatic failure have been reported with dipyridamole. No dosage adjustment is needed for mild to moderate hepatic impairment with prasugrel. While prasugrel has not been studied in severe hepatic impairment, these patients are generally at higher risk of bleeding. Impaired hepatic function can increase risk of adverse events, such as bleeding for ticagrelor. Ticagrelor use should be avoided in patients with severe hepatic impairment and should be considered carefully in patients with moderate impairment. No dosage adjustment of ticagrelor is needed in patients with mild hepatic impairment. Based on the increased inherent risk of bleeding in patients with severe hepatic impairment, vorapaxar is not recommended in such patients.

Geriatrics

No dosage adjustment is recommended for elderly patients taking clopidogrel, dipyridamole, aspirin/omeprazole DR, or vorapaxar.

The risk of bleeding with use of prasugrel increases with advancing age. According to the manufacturer's label, for patients 75 years of age and older, the use of prasugrel is not recommended except in high-risk situations, such as the presence of diabetes or history of MI. However, ACCP states in their 2012 guidelines that evidence suggests that prasugrel results in no net benefit or even harmed patients with age greater than 75 years.[164]

No overall differences in safety or effectiveness of ticagrelor have been observed between patients ≥ 65 years of age and younger patients; however, greater sensitivity of some older individuals cannot be ruled out. Relative risk of bleeding was similar in patients ≥ 65 years of age and those ≥75 years of age. Efficacy and overall safety of ticagrelor in high-risk patients including elderly patients (≥ 75 years old) with ACS and those with prior history of stroke or TIA were consistent with the overall PLATO trial.[165,166]

Race

Asian patients have approximately a 4-fold higher exposure to omeprazole than Caucasians, which is thought to be related to CYP2C19 metabolism. Approximately 15% to 20% of Asians are CYP2C19 poor metabolizers. Avoid use of aspirin/omeprazole DR in Asian patients with an unknown CYP2C19 genotype or those who are known poor metabolizers.

DOSAGES[167,168,169,170,171,172,173]

Drug	Dose	Availability
aspirin 25 mg/ dipyridamole ER 200 mg	1 capsule twice daily Alternative regimen for patients with intolerable headaches: during initial treatment, switch to 1 capsule at bedtime and low-dose aspirin in the morning Because there are no outcomes data with this regimen and headaches become less of a problem as treatment continues, patients should return to the usual regimen (1 capsule twice daily) as soon as possible, usually within 1 week	25 mg/200 mg capsule The fixed-dose combination product is not interchangeable with the individual components of aspirin and dipyridamole tablets
aspirin/omeprazole DR (Yosprala)	1 tablet once daily at least 60 minutes prior to a meal Swallow whole; do not split, chew, crush, or dissolve tablet	81 mg/40 mg, 325 mg/40 mg tablets Yosprala is not interchangeable with its individual components
clopidogrel (Plavix)	Recent MI, recent stroke, established PAD: 75 mg daily Acute coronary syndrome: 300 mg for 1 dose then 75 mg daily	75 mg, 300 mg tablets
dipyridamole	75 to 100 mg 4 times daily with concurrent coumarin anticoagulants	25 mg, 50 mg, 75 mg tablets
prasugrel (Effient)	60 mg for 1 dose then 10 mg daily plus aspirin 75 to 325 mg daily	5 mg, 10 mg tablets
ticagrelor (Brilinta)	ACS or history of MI: ticagrelor 180 mg for first dose, then 90 mg twice daily thereafter for the first year, followed by 60 mg twice daily thereafter After initial aspirin loading dose (usually 325 mg), use ticagrelor with a daily maintenance dose of aspirin of 75-100 mg Do not use with aspirin doses > 100 mg/day CAD but no prior stroke or MI: 60 mg of ticagrelor twice daily; use with a daily maintenance dose of aspirin of 75-100 mg Acute ischemic stroke or TIA: ticagrelor 180 mg loading dose, then 90 mg twice daily for up to 30 days (treatment effect accrued early in the course of therapy); use with a loading dose of aspirin (300-325 mg) and a daily maintenance dose of aspirin of 75-100 mg For those unable to swallow, tablets may be crushed and mixed with water, then consumed or administered through a nasogastric tube	60 mg, 90 mg tablets
vorapaxar (Zontivity)	2.08 mg daily*	2.08 mg tablet

* There is no experience with use of vorapaxar alone as the only administered antiplatelet agent. Vorapaxar has been studied only as an addition to aspirin and/or clopidogrel and should only be used with aspirin and/or clopidogrel according to their indications or standard of care.[174]

Pretreatment with clopidogrel therapy can reduce the risks associated with PCI. A loading dose of 600 mg instead of 300 mg has been studied in an effort to determine if this higher loading dose would

shorten the time for clopidogrel to become effective and produce a greater antiplatelet effect, without an apparent adverse effect on safety.[175,176,177,178,179,180,181,182] Current recommendations recommend a loading dose of 600 mg of clopidogrel in patients undergoing PCI; however, this is not an FDA-approved dose.[183]

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled trials comparing agents in ambulatory patients who are at high risk or have documented vascular disease due to thrombotic episodes are considered the most relevant in this category. Studies included also reflect the FDA-approved indications. Comparative trials are the most important, but when comparative trials are not available, placebo-controlled trials were considered relevant. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance. Several trials have established the role of these agents for their respective indications; thus, inclusion of newer comparative clinical trials within this class also considers the clinical impact of their findings.

aspirin

Aspirin has been extensively studied and found to prevent vascular events, both fatal and non-fatal, by 15% to 30% in many trials.[184] The Physicians' Health Study with 22,071 men (age > 50 years without CAD) provided the first strong support for aspirin 325 mg daily in reducing the risk of a first MI; however, the relative risk reductions for stroke and mortality due to CV causes were less clear.[185] Further study confirmed aspirin use also reduced mortality in patients at higher risk for CV disease.[186,187]

The Women's Health Study was a large randomized, double-blind, placebo-controlled trial of aspirin 100 mg daily in the primary prevention of CV disease among 39,876 healthy women, with a majority of women less than age 65 years.[188] Patients were followed for a mean of 10 years for the major CV events of MI, stroke, and death from CV causes. The risk of major CV events was slightly lower with aspirin; however, the risk reduction was not statistically significant (9% relative risk reduction, 0.91; 95% CI, 0.8 to 1.03; p=0.13). Aspirin reduced the relative risk of stroke by 17% (RR, 0.83; 9% CI, 0.69 to 0.99; p=0.04) but not of MI.

The findings from the large preventive trials—Physician's Health Study in men and Women's Health Study—differ. Aspirin doses and rate of MI are examples of the many differences between the 2 studies. Aspirin therapy was associated with a 32% reduction in MI but no significant effect on stroke in men.[189]

aspirin/dipyridamole ER

The second European Stroke Prevention Study (ESPS-2) evaluated the effectiveness of dipyridamole ER plus low-dose aspirin in the secondary prevention of stroke versus monotherapy for 2 years.[190] The double-blind study randomized 6,602 patients who had experienced a TIA or ischemic stroke within the previous 3 months to placebo, aspirin 25 mg twice daily, dipyridamole ER 200 mg twice daily, or the combination of aspirin 25 mg plus dipyridamole ER 200 mg twice daily. The primary endpoints were stroke, death, or the combination. The aspirin/dipyridamole ER group showed a relative risk reduction for stroke of 37% versus placebo (p<0.001), 18% with ASA alone (p=0.013), and 16% with dipyridamole alone (p=0.039). The combination therapy had an absolute risk reduction of fatal and nonfatal stroke of 3% versus aspirin and dipyridamole monotherapy groups. Mortality rate was not significantly affected by any treatment. Beneficial effects of antiplatelet therapy were evident regardless of age.[191] Aspirin was associated with significantly more overall and gastrointestinal bleeding compared to dipyridamole or placebo.

In a randomized, placebo-controlled study of 149 patients from fibrinolytic trials who had a patent infarct-related artery 3 to 4 weeks after STEMI, quantitative coronary angiography of non-infarct arteries was performed on paired cine-angiograms at 1 year.[192] Patients had been randomized to either continue the daily combination of 50 mg aspirin and 400 mg dipyridamole or to placebo. There were no significant differences in these groups in changes in minimal luminal diameter (MLD) (-0.02 mm; 95% CI, -0.09 to 0.05). Progression of CAD was seen in two-thirds of patients and did not independently predict long-term death and/or reinfarction.

aspirin/omeprazole DR (Yosprala)

The efficacy of aspirin has been described above. Two randomized, multicenter, double-blind trials established the role of omeprazole in this combination product by comparing daily aspirin/omeprazole DR 325 mg/40 mg to enteric-coated aspirin 325 mg to determine the rate of gastric ulcer formation (n=1,049).[193] Patients included were actively taking aspirin 325 mg/day, ≥ 55 years old, and were expected to be on aspirin therapy of at least 6 months. Adults younger than 55 years were also included if they had a documented gastric or duodenal ulcer within the past 5 years. Notably, approximately 11% were also receiving at least 1 NSAID. After 6 months, gastric ulcers occurred in 3.8% of patients in the aspirin/omeprazole DR group compared to 8.7% of patients in the aspirin group in Study 1 (p=0.02). In Study 2, gastric ulcers occurred in 2.7% of patients in the aspirin/omeprazole DR group compared to 8.5% of patients in the aspirin group (p=0.005).

clopidogrel (Plavix) versus aspirin

In the CAPRIE study, clopidogrel 75 mg daily and aspirin 325 mg daily were compared for relative efficacy in reducing a composite outcome cluster of ischemic stroke, MI, or vascular death in a randomized, blinded trial.[194] A total of 19,185 patients with a documented stroke, MI, or symptomatic peripheral arterial disease were enrolled in the trial and followed for 1 to 3 years. Significant findings include an 8.7% relative risk reduction of all endpoints (ischemic stroke, MI, or vascular death) with clopidogrel (5.32% annual risk) versus aspirin (5.83% annual risk) (95% Cl, 0.3 to 16.5; p=0.043). The absolute risk reduction of clopidogrel over aspirin was 0.5% for the combined endpoints. Hemorrhagic events were similar between the groups.[195]

clopidogrel (Plavix) plus aspirin

The CURE study evaluated the efficacy and safety of clopidogrel when given with aspirin in 12,562 acute coronary syndrome patients.[196] Patients were randomized within 24 hours of onset of angina symptoms to clopidogrel 300 mg for 1 dose then 75 mg daily or placebo, in addition to aspirin (75 to 325 mg daily), for 3 to 12 months. The composite primary endpoint was CV death, nonfatal MI, or stroke, which occurred in 9.3% of the clopidogrel group and 11.4% in the placebo group (RR with clopidogrel as compared with placebo, 0.8; 95% CI, 0.72 to 0.9; p<0.001). Clopidogrel reduced the risk of the second primary endpoint defined as the composite of CV death, nonfatal MI, or stroke or the occurrence of refractory ischemia compared to the placebo group (16.5% clopidogrel group compared to 18.8% in the placebo group; RR, 0.86; 95% CI, 0.79 to 0.94; p<0.001). Rates of the individual outcome endpoints of CV death, stroke, and refractory ischemia showed numerical improvement with clopidogrel but did not achieve statistical significance. Significantly more major bleeding episodes were observed in the clopidogrel group (3.7% in the clopidogrel group versus 2.7% in the placebo group, relative risk 1.38; p=0.001). Hemorrhagic strokes and life-threatening bleeding episodes were similar in both groups. Higher doses of aspirin with or without clopidogrel were associated with a higher risk of major bleeding.[197] Minor bleeding episodes were significantly higher in the clopidogrel group (5.1% versus 2.4% in the placebo group, p<0.001). Benefits of the combination of clopidogrel and aspirin are seen at all doses of aspirin; however, bleeding risk increased with higher doses of aspirin.[198]

In an evaluation of the 2,658 patients that underwent PCI after randomization in the CURE study (PCI-CURE study), clopidogrel and placebo in addition to aspirin were compared for safety and efficacy.[199] Patients received aspirin and the study drug (clopidogrel or placebo) for a median of 10 days prior to PCI. Open-label use of ticlopidine (no longer available) or clopidogrel in addition to aspirin 75 to 325 mg daily was permitted for 2 to 4 weeks after stent placement and then the randomly assigned medication resumed for a mean of 8 months. The primary endpoint was the composite of CV death, MI, or urgent revascularization within 30 days of the PCI. The rate of composite endpoint in the clopidogrel group was 4.5% compared to 6.4% in the placebo group within the first 30 days (RR, 0.7; 95% CI, 0.5 to 0.97; p=0.03). As seen in the CURE study, clopidogrel patients had a lower incidence of CV death and MI or any revascularization compared to placebo (p=0.03) and a lower rate of CV death or MI (p=0.047). Bleeding rates between the groups did not differ significantly.

The COURAGE trial was a randomized, multicenter, 4.6-year study of 2,287 patients with stable CAD.[200] Patients underwent PCI plus optimal medical therapy (PCI group) or optimal medical therapy alone. All patients received aspirin 81 to 325 mg per day or clopidogrel 75 mg per day, if patients were intolerant to aspirin. Patients undergoing PCI received both aspirin and clopidogrel. Both groups received beta blockers, statins, ACE inhibitors, as well as made lifestyle modifications of diet, exercise, and smoking cessation. The median follow-up period was 4.6 years. The primary outcome of death from any cause and nonfatal MI occurred in 19% of the PCI group versus 18.5% of the optimal medical therapy group (hazard ratio [HR], 1.05; 95% CI, 0.87 to 1.27; p=0.62). More patients in the optimal medical therapy group required revascularization (32.6%) versus the PCI group (21.1%; p<0.001). PCI had the initial advantage of relieving angina; however, 74% of the PCI group versus 72% of the optimal medical therapy group did not experience angina at 5 years (p=0.35). PCI did not reduce the risk of death, MI, or other major CV events in comparison to optimal medical therapy in patients with stable CAD.

In the CREDO study, 2,116 patients who planned to have angioplasty were randomized to clopidogrel or placebo and followed for 1 year for the combined event rate of death, MI, or stroke.[201] In the

double-blind, placebo-controlled trial, patients randomized to clopidogrel received 300 mg prior to the revascularization or placebo. All patients received aspirin 325 mg daily and clopidogrel 75 mg daily for 28 days following stent placement. On day 29, patients then received clopidogrel or placebo, in addition to aspirin, as randomized prior to revascularization. At 1 year, 8.5% of the clopidogrel group had reached the composite endpoint (death, MI, or stroke at 1 year) compared to 11.5% in the placebo group (26.9% relative risk reduction; 95% CI, 3.9 to 44.4; p=0.02). Clopidogrel was not associated with a significant reduction in the combined event rate of death, MI, or urgent target vessel revascularization at 28 days. No significant difference was seen in the individual endpoints (death, MI, or death/MI) or bleeding over the 1-year study period. During 1 year of follow-up, any bleeding (major or minor) occurred in 8.1 and 8.9%, major bleeding in 3.9 and 5.6%, and minor bleeding in 4.2% and 3.3% of placebo and clopidogrel treated patients, respectively.[202] These differences were not significant. Major GI bleeding occurred in significantly more patients on clopidogrel compared to placebo (1.4 versus 0.3%; p=0.011).

In the MATCH trial, in patients who were already on clopidogrel 75 mg daily, the addition of aspirin 75 mg daily was compared to placebo to see if the combination had a greater benefit in preventing vascular events and to assess the potential for increased bleeding risk over 18 months.[203] The study was a randomized, double-blind, placebo-controlled trial in 7,599 high risk patients having had a recent ischemic stroke or TIA and at least 1 additional risk factor who were already receiving clopidogrel therapy. The primary endpoint was a composite of ischemic stroke, MI, vascular death, or rehospitalization for acute ischemic attack (TIA, angina, worsening PAD). The primary endpoint was seen in 15.7% of the aspirin/clopidogrel group and 16.7% in the clopidogrel alone group (relative risk reduction of 6.4%; 95% CI, -0.46 to 16.3; absolute risk reduction 1%; 95% CI, -0.6 to 2.71). Combination therapy with clopidogrel and aspirin did not reduce the risk of major vascular events compared with clopidogrel monotherapy. The combination of aspirin and clopidogrel was associated with a higher rate of life-threatening bleeding episodes (2.6%) compared to clopidogrel monotherapy (1.3%). Major bleeding episodes were more common with the combination; however, mortality was unaffected.

CLARITY-TIMI-28 study: Clopidogrel was evaluated for safety and efficacy in the treatment of STEMI in addition to standard treatment of fibrinolytics, aspirin, and weight-dosed heparin.[204] Patients were scheduled to undergo angiography 48 to 192 hours after the start of the study medication. Patients between ages 18 and 75 years (n=3,491) who presented within 12 hours of ST-elevation were randomized to clopidogrel 300 mg loading dose then 75 mg daily or placebo. The rates of primary efficacy endpoint of composite of angiography identified occluded infarct-related arteries (thrombolysis in myocardial infarction [TIMI] flow grade 0 or 1) or death or recurrent MI before angiography was reported in 21.7% of patients in the placebo group and 15% of patients in the clopidogrel group (6.7% difference; 95% CI, 24 to 47%; p<0.001). After 30 days, clopidogrel had a relative risk reduction of 20% for the composite of CV death, recurrent MI, or recurrent ischemia requiring revascularization (14.1% placebo versus 11.6% clopidogrel; p=0.03). Death from CV causes was similar between the groups and extremely low for the STEMI population (2.6% and 2.2% for clopidogrel and placebo groups, respectively; p=0.49). Incidences of major bleeding (1.3% and 1.1% for clopidogrel and placebo groups, respectively) and intracranial hemorrhage were similar in both groups.

The PCI-CLARITY trial evaluated if pre-treatment with clopidogrel in the setting of PCI in patients with recent ST-segment elevation MI would affect the rate of major adverse CV events.[205] Patients (n=1,863) were those who underwent PCI after the required angiography as a part of the CLARITY trial

discussed above. In the double-blind, placebo-controlled trial, patients received aspirin and were randomized to receive clopidogrel 300 mg once then 75 mg daily or placebo in addition to the fibrinolytics and weight-based heparin for 2 to 8 days until angiography. In patients undergoing PCI with stenting, open-labeled clopidogrel including the loading dose were administered after the angiography but prior to PCI. The primary outcome was the composite of CV death, MI, or stroke from date of PCI to 30 days after randomization. Pre-treatment with clopidogrel was associated with a significant reduction in the composite outcome (3.6% versus 6.2%, adjusted odds ratio [OR], 0.54; 95% CI, 0.35 to 0.85; p=0.008). From randomization to 30 days, the clopidogrel group had a significant reduction in CV death, MI, or stroke (7.5 %versus 12%; adjusted OR 0.59; 95% CI, 0.43 to 0.81; p=0.001). Bleeding was not significantly different between the groups. Authors concluded that aspirin plus clopidogrel in addition to fibrinolytics and heparin reduce the composite outcome and should be administered prior to and after PCI.

The CURRENT-OASIS 7 investigated doubling the loading dose (from 300 mg to 600 mg) and the initial maintenance dose (from 75 mg to 150 mg) of clopidogrel for 1 week followed by 75 mg daily thereafter, with high (300 to 325 mg) or low dose (75 to 100 mg) aspirin daily in patients (n=25,086) with ST or non-ST-segment-elevation ACS managed with an early invasive strategy.[206,207,208] There was no significant difference between high dose and standard dose clopidogrel (4.2% versus 4.4%; hazard ratio [HR] 0.94; 95% CI, 0.83 to 1.06; p=0.3) for the primary outcome of CV death, MI, or stroke at 30 days. However, high dose clopidogrel was associated with a significant reduction in the secondary outcome of stent thrombosis among patients who underwent PCI (n=17,263; 1.6% versus 2.3%; HR, 0.68; 95% CI, 0.55 to 0.85; p=0.001). The primary safety endpoint of major bleeding was significantly greater for the high-dose group compared to the standard regimen (2.5% versus 2%; HR, 1.24; 95% CI, 1.05 to 1.46; p=0.01). There was no significant difference between higher-dose and lower-dose aspirin with respect to the primary outcome (4.2% versus 4.4%; HR, 0.97; 95% CI, 0.86 to 1.09; p=0.61) or major bleeding (2.3% versus 2.3%; HR, 0.99; 95% CI, 0.84 to 1.17; p=0.9).

In the CHARISMA trial, clopidogrel and aspirin were compared to aspirin alone in the prevention of the composite endpoint of MI, stroke, or CV death in a population of patients at high risk for CV diseases.[209] In the prospective, double-blind, randomized trial, a total of 15,603 patients with a history of CV disease or multiple risk factors were randomized to clopidogrel 75 mg daily plus aspirin 75 to 162 mg daily or placebo plus aspirin 75 to 162 mg daily. After a median of 28 months, 6.8% of the clopidogrel-aspirin group and 7.3% of the placebo-aspirin group reported the primary endpoint (RR, 0.93; 95% CI, 0.83 to 1.05; p=0.22). The clopidogrel-aspirin group had significantly fewer patients report the secondary efficacy endpoint of the composite of MI, stroke, CV-related death, or hospitalizations due to unstable angina, TIA, or revascularization procedures (clopidogrel-aspirin, 16.7%; placebo-aspirin, 17.9%; RR 0.92; 95% CI, 0.86 to 0.995; p=0.04). A subgroup analysis found that patients with only risk factors (approximately 20% of total population) had a higher risk of death from all causes (5.4% versus 3.8%; p=0.04) and CV death (3.9% versus 2.2%; p=0.01) with both drugs than with aspirin alone. Those with established CV disease (nearly 80% of total population) had a lower risk in the primary endpoint with clopidogrel (6.9% versus 7.9% with placebo; RR, 0.88; 95% CI, 0.77 to 0.998; p=0.046). The rate of severe bleeding was similar in both treatment groups with 1.7% and 1.3% for clopidogrel-aspirin and placebo-aspirin groups, respectively (RR, 1.25; 95% CI, 0.97 to 1.61%; p=0.09). Moderate bleeding occurred more often in patients on the combination therapy (2.1% versus 1.3%; RR 1.62; 95% CI, 1.27 to 2.1; p<0.001). The rate of intracranial hemorrhage was similar in the 2

treatment groups. Treatment discontinuation was reported in 20.4 and 18.2% of the clopidogrel-aspirin versus placebo-aspirin groups, respectively (p<0.001).

The COMMIT trial was a randomized, double-blinded trial in which the combination of clopidogrel and aspirin was compared to aspirin alone in 45,852 patients with suspected acute MI in 1,250 sites in China.[210] Patients were randomized within 24 hours of suspected acute MI to clopidogrel 75 mg daily or placebo in addition to aspirin 162 mg daily until discharge or up to 4 weeks in the hospital. ST-segment elevation or bundle branch block was noted in 93% of patients, and ST-segment depression was noted in the remaining 7%. Fibrinolysis was administered in half of the patients. Metoprolol use was also being evaluated in the same population. The 2 primary endpoints were (1) the composite of death, reinfarction, or stroke and (2) death from any cause. Clopidogrel-aspirin combination significantly reduced the risk of the composite of death, reinfarction, or stroke compared to aspirin alone (clopidogrel, 9.2% [n=2,125] versus aspirin alone, 10.1% [n=2,311]; p=0.002). All-cause mortality by hospital discharge was significantly lower in the clopidogrel group (7.5% versus 8.1%; p=0.03). Any type of major bleed (fatal, transfused, and cerebral bleeds) occurred in 0.58 and 0.55% of the clopidogrel-aspirin and placebo-aspirin groups, respectively (p=not significant [NS]).

The Randomized Argentine Clopidogrel Stent (RACS) trial was a prospective, randomized, non-blinded study of 1,004 patients undergoing PCI who were randomized after successful bare metal stent (BMS) placement to 30 versus 180 days of clopidogrel.[211] All patients also received aspirin. The primary endpoint was a composite of death, MI, and stroke at 180 days. At hospital discharge and 30 days (when both arms received the same treatment), there were no significant differences in frequency of death, MI, or stroke. In comparison from 30 days to 180 days, the patients in the 180 days of clopidogrel reached the primary endpoint (death, MI, and stroke) less frequently (4.99% versus 1.74%; 65% relative risk reduction; p=0.01). No significant differences in frequency of total bleeding were reported.

Data from consecutive acute STEMI survivors and either concomitant therapy with aspirin or aspirin plus clopidogrel at discharge, who were prospectively enrolled in the Acute Coronary Syndromes (ACOS) registry, were analyzed.[212] The 5,886 patients were divided into 3 groups based on the initial reperfusion therapy (no reperfusion therapy n=1,445; fibrinolysis n=1,734; or primary PCI n=2,707). Mortality was significantly lower in the clopidogrel plus aspirin group versus the aspirin group in the total group, as well as the reperfusion therapy [total group OR, 0.48; 95% CI, 0.48 to 0.61; no reperfusion therapy OR, 0.96; 95% CI, 0.65 to 1.45; fibrinolysis OR, 0.53; 95% CI, 0.32 to 0.87; primary PCI OR, 0.38; 95% CI, 0.23 to 0.62].

clopidogrel (Plavix) versus aspirin/dipyridamole ER

The PRoFESS study was a randomized, double-blind, 2-by-2 factorial design, multicenter secondary stroke prevention trial.[213] A total of 20,332 patients, who had a noncardioembolic ischemic stroke within the previous 120 days, were randomized to aspirin 25 mg/dipyridamole ER 200 mg twice daily or to clopidogrel 75 mg daily and followed for a mean of 2.5 years. The comparison for the primary outcome of recurrent stroke did not meet the pre-defined criterion for non-inferiority (margin of 1.075 or a 75% noninferiority difference), and the number of recurrent strokes was similar between groups: recurrent stroke occurred in 9% and 8.8% of patients receiving aspirin/dipyridamole ER and clopidogrel, respectively (HR, 1.01; 95% CI, 0.92 to 1.11). The secondary outcome of composite stroke, MI, or vascular death was identical between groups: 13.1% in each group (HR for aspirin/dipyridamole

ER, 0.99; 95% CI, 0.92 to 1.07). More major hemorrhagic events were reported in the aspirin/dipyridamole ER group compared to clopidogrel, 4.1% versus 3.6%, respectively (HR, 1.15; 95% CI, 1 to 1.32), including intracranial hemorrhage (HR, 1.42; 95% CI, 1.11 to 1.83). Despite the increase in hemorrhage, the net risk of recurrent stroke or major hemorrhagic events was similar in both groups: aspirin/dipyridamole ER 11.7% compared with clopidogrel 11.4% (HR, 1.03; 95% CI, 0.95 to 1.11).

dipyridamole

Very little new clinical data are available for dipyridamole monotherapy. Older data with dipyridamole provides evidence that in patients with prosthetic heart valves, the addition of dipyridamole to warfarin therapy reduces the incidence of systemic emboli.[214] It should be noted that the extended-release dipyridamole formulation, not immediate-release dipyridamole, was used in the ESPS-2 and ESPIRIT trials.[215,216]

prasugrel (Effient) versus clopidogrel (Plavix)

TRITON-TIMI 38: To compare prasugrel with clopidogrel, 13,608 patients with moderate to high-risk acute ACS with scheduled PCI were randomized to receive prasugrel (60 mg loading dose, then 10 mg daily) or clopidogrel (300 mg loading dose, then 75 mg daily) for 6 to 15 months.[217] The primary efficacy endpoint was death from CV causes, nonfatal MI, or nonfatal stroke. The key safety endpoint was major bleeding. The primary endpoint occurred in 12.1% of patients receiving clopidogrel and 9.9% of patients receiving prasugrel (HR versus clopidogrel, 0.81; 95% CI, 0.73 to 0.9; p<0.001). There were also significant reductions in the prasugrel group in the rates of MI (9.7% versus 7.4%; p<0.001), urgent target-vessel revascularization (3.7% versus 2.5%; p<0.001), and stent thrombosis (2.4% versus 1.1%; p<0.001). Prasugrel patients experienced more major bleeding than those on clopidogrel (2.4% versus 1.8%; HR, 1.32; 95% CI, 1.03 to 1.68; p=0.03). Life-threatening bleeding (1.4% versus 0.9%; p=0.01), including nonfatal bleeding (1.1% versus 0.9%; p=0.23) and fatal bleeding (0.4% versus 0.1%; p=0.002), was also higher with prasugrel. The rate of study drug discontinuation because of adverse reactions was 7.2% for prasugrel and 6.3% for clopidogrel. Bleeding was the most common adverse reaction leading to study drug discontinuation for both drugs (2.5% for prasugrel and 1.4% for clopidogrel).

In patients undergoing PCI for STEMI, TIMI life-threatening bleeding and TIMI major or minor bleeding were similar with the 2 treatments. Only TIMI major bleeding after CABG surgery was significantly increased with prasugrel versus clopidogrel, 18.8% versus 2.7%, respectively (p=0.0033).[218] A post-hoc analysis of TRITON-TIMI 38 evaluated the efficacy and safety of prasugrel and clopidogrel in the setting of a glycoprotein (GP) IIb/IIIa inhibitor at 30 days.[219] A total of 54.5% received a GP IIb/IIIa inhibitor. There was a consistent benefit of prasugrel over clopidogrel for reducing CV death, MI, or stroke in patients who did (HR, 0.76; 95% CI, 0.64 to 0.9) or did not receive a GP IIb/IIIa inhibitor (HR, 0.78; 95% CI, 0.63 to 0.97, p=0.83). Although subjects treated with a GP IIb/IIIa inhibitor had greater rates of bleeding, the risk of major or minor bleeding with prasugrel versus clopidogrel was not significantly different in patients who were or were not treated with GP IIb/IIIa inhibitor (p=0.19).

A pre-specified analysis compared prasugrel with clopidogrel in patients with diabetes mellitus (DM) in TRITON-TIMI 38.[220] A total of 3,146 subjects had a preexisting history of DM including 776 receiving insulin. The primary endpoint was reduced significantly with prasugrel among subjects without DM (9.2% versus 10.6%; HR, 0.86; p=0.02) and with DM (12.2% versus 17%; HR, 0.7; p<0.001). A benefit for prasugrel was observed among DM patients on insulin (14.3% versus 22.2%; HR, 0.63; p=0.009) and

those not on insulin (11.5% versus 15.3%; HR, 0.74; p=0.009). MI was reduced with prasugrel by 18% among subjects without DM (7.2% versus 8.7%; HR, 0.82; p=0.006) and by 40% among subjects with DM (8.2% versus 13.2%; HR, 0.6; p<0.001). The TIMI major hemorrhage was increased among subjects without DM on prasugrel (1.6% versus 2.4%; HR, 1.43; p=0.02), but the rates were similar among subjects with DM for clopidogrel and prasugrel (2.6% versus 2.5%; HR, 1.06; p=0.81). Net clinical benefit (death, nonfatal myocardial infarction, nonfatal stroke, and nonfatal TIMI major bleeding) with prasugrel was greater for DM patients (14.6% versus 19.2%; HR, 0.74; p=0.001) than for patients without DM (11.5% versus 12.3%; HR, 0.92; p=0.16).

TRILOGY ACS: In a randomized, double-blind trial, patients with UA/NSTEMI and receiving aspirin, who did not undergo revascularization, were evaluated for up to 30 months of treatment with prasugrel versus clopidogrel 75 mg.[221] Patients randomized to prasugrel who were under 75 years of age received 10 mg daily (n=7,243), while those 75 years of age and older received 5 mg daily (n=2,083). Median exposure to study drug was 14.8 months. Primary endpoint was death from CV causes, MI, or stroke. At a median follow-up of 17 months, the primary endpoint occurred in 13.9 of patients receiving prasugrel and 16% receiving clopidogrel (HR, 0.91; 95% CI, 0.79 to 1.05; p=0.21). Results were similar regardless of age. At 30 months, there was no significant difference between the study groups in occurrence rate of primary endpoint. While there was no difference in the rate of the primary composite endpoint or its separate components between the 2 study groups in the first year of the study, the investigators found that prasugrel appeared to reduce the risk of events from 12 months onward; hazard ratio for the time period of ≤ 12 months versus the time period > 12 months comparing prasugrel with clopidogrel for the primary efficacy endpoint were 0.99 (95% CI, 0.84 to 1.16) versus 0.72 (95% CI, 0.54 to 0.97; p=0.07 for interaction). There was no significant difference in the rate of severe, major, or life-threatening bleeding between the 2 study groups. A subsequent analysis which evaluated the CYP2C19 metabolizer status of enrolled patients found that this was not associated with the composite endpoint; however, CYP2C19 metabolizer status was not available for all those enrolled in the TRILOGY ACS trial.[222]

ticagrelor (Brilinta) versus clopidogrel (Plavix)

The study of Platelet Inhibition and Patient Outcomes (PLATO) was a randomized, double-blind trial that compared ticagrelor and clopidogrel for the prevention of CV events in 18,624 patients admitted to the hospital with an acute coronary syndrome (ACS), unstable angina, and myocardial infarction with or without ST-segment elevation.[223] Patients were randomized to receive ticagrelor 180 mg loading dose, 90 mg twice daily thereafter, or clopidogrel 300 mg loading dose, 75 mg daily thereafter. All patients also received a maintenance dose of aspirin (75 to 100 mg recommended). The primary endpoint was a composite of death from vascular causes, MI, or stroke. At 12 months, the primary endpoint had occurred in 9.8% of patients receiving ticagrelor and 11.7% of those receiving clopidogrel (HR, 0.84; 95% CI, 0.77 to 0.92; p<0.001). Secondary endpoints of MI alone occurred in 5.8% in the ticagrelor group and 6.9% in the clopidogrel group (p=0.005); and death from vascular causes occurred in 4% versus 5.1%, respectively (p=0.001). There was no significant difference in stroke alone between the 2 groups (1.5% versus 1.3%, respectively; p=0.22). The rate of death from any cause was also reduced with ticagrelor (4.5% versus 5.9% with clopidogrel; p<0.001). No significant difference in the rates of major bleeding was found between the ticagrelor and clopidogrel groups (11.6% and 11.2%, respectively; p=0.43), but ticagrelor was associated with a higher rate of major bleeding not related to CABG (4.5% versus 3.8%; p=0.03), including more instances of fatal intracranial bleeding and fewer fatal bleeding of

other types. In PLATO, use of > 100 mg of aspirin decreased the effectiveness of ticagrelor. In the North American (mostly US) PLATO subgroup, ticagrelor was numerically inferior to clopidogrel. Among 11,289 patients with PCI receiving any stent during PLATO, there was a lower risk of definite stent thrombosis for ticagrelor than with clopidogrel. The results were similar for drug-eluting and bare metal stents.

ticagrelor (Brilinta) versus aspirin

SOCRATES, a multinational, double-blind, randomized trial, compared the efficacy of ticagrelor and aspirin for secondary prevention of recurrent stroke and CV events in 13,199 patients with a nonsevere ischemic stroke or high-risk TIA.[224] Patients who had not received intravenous or intraarterial thrombolysis and without a cardioembolic stroke were randomized 1:1 within 24 hours of symptom onset to either ticagrelor (180 mg on day 1 and 90 mg twice daily thereafter) or aspirin (300 mg on day 1 and 100 mg daily thereafter) for 90 days. The primary outcome was the composite endpoint of time to occurrence of stroke, MI, or death, which occurred in 6.7% of patients treated with ticagrelor compared to 7.5% of patients treated with aspirin (HR, 0.89; 95% CI, 0.78 to 1.01; p=0.07). Major bleeding occurred in 0.6% of patients treated with aspirin compared to 0.5% of those treated with ticagrelor (HR, 0.83; 95% CI, 0.52 to 1.34; p=0.45). Thus, the authors concluded that ticagrelor was not superior to aspirin in decreasing stroke, MI, or death at 90 days in select patients with a prior stroke or TIA. Notably, ticagrelor is not approved for prevention of stroke or CV-related events in patients with a prior stroke or TIA.

ticagrelor (Brilinta) plus aspirin versus placebo plus aspirin

THEMIS (NCT01991795), a randomized, placebo-controlled, double-blind study, evaluated the efficacy of ticagrelor and aspirin in patients ≥ 50 years of age with stable CAD and T2DM.[225] A total of 19,220 patients were randomized 1:1 to receive either ticagrelor plus aspirin (n=9,619) or placebo plus aspirin (n=9,601). Patients with prior MI or stroke were excluded. The dose of ticagrelor was initially 90 mg twice daily but the protocol was amended based on results of the PEGASUS–TIMI 54, and the dose of ticagrelor was decreased to 60 mg twice daily. Patients in both study arms also received low-dose aspirin (75 mg to 150 mg) unless there was a contraindication or unacceptable adverse effect. The primary efficacy endpoint was a composite of CV death, MI, or stroke and was found to be significantly lower with ticagrelor (7.7%) than with placebo (8.5%) (hazard ratio [HR], 0.9; 95% CI, 0.81 to 0.99; p=0.04). However, the primary safety endpoint of major bleed as defined by the Thrombolysis in Myocardial Infarction (TIMI) criteria was higher with ticagrelor than with placebo (2.2% versus 1%, respectively; HR, 2.32; 95% CI, 1.82 to 2.94; p<0.001). Furthermore, the incidence of intracranial hemorrhage was also increased with ticagrelor compared to placebo (0.7% versus 0.5%, respectively; HR, 1.71; 95% CI, 1.18 to 2.48; p=0.005). For the endpoint assessing fatal bleeding, there was not a significant difference between the 2 study arms (0.2% versus 0.1%, respectively; HR, 1.9; 95% CI, 0.87 to 4.15; p=0.11).

ticagrelor (Brilinta) plus aspirin versus placebo plus aspirin

THALES (NCT03354429), a randomized, placebo-controlled, double-blind study, evaluated the efficacy of ticagrelor and aspirin in patients who had experienced a mild-to-moderate acute noncardioembolic ischemic stroke or TIA.[226] A total of 11,016 patients with a NIH stroke scale score of ≤ 5 (range, 0 to 42, higher scores for more severe stroke) or TIA. Patients were not receiving thrombolysis or thrombectomy and were randomized within 24 hours of symptom onset 1:1 to either a 30-day regimen of ticagrelor (180 mg loading dose, then 90 mg twice daily) in combination with aspirin (300 mg to 325 mg loading dose, then 75 mg to 100 mg daily) or matching placebo in combination with aspirin. A total of 5,523

patients were assigned to the ticagrelor plus aspirin group and 5,493 to the aspirin only arm. The primary endpoint was the composite of stroke or death within 30 days and occurred in 5.5% (n=303) of patients who received ticagrelor plus aspirin compared to 6.6% (n=362) of patients in the aspirin study arm corresponding to a hazard ratio (HR) of 0.83 (95% CI, 0.71 to 0.96; p=0.02). The secondary endpoint of first subsequent ischemic stroke was also significantly reduced with ticagrelor plus aspirin compared to aspirin only (5% versus 6.3%, respectively; HR, 0.79; 95% CI, 0.68 to 0.93; p=0.004); however, the secondary endpoint assessing incidence of disability within 30 days was not significantly different between study arms. Severe bleeding was evaluated as the primary safety outcome and occurred in 0.5% (n=28) in the ticagrelor plus aspirin group compared with 0.1% (n=7) in the aspirin only group (p=0.001).

vorapaxar (Zontivity)

A multicenter, randomized, double-blind, placebo-controlled study (TRA 2P – TIMI) compared vorapaxar to placebo.[227,228] There are 2 important differences between data in the TRA 2P publication and the approved prescribing information. The original cohort included patients with a history of MI (≥ 2 weeks but ≤ 12 months prior), ischemic stroke, or peripheral artery disease (PAD; history of intermittent claudication and an ankle-brachial index of < 0.85, or amputation or revascularization of the extremities secondary to ischemia). During the trial, after a median of 24 months of follow-up, an increased risk of intracerebral hemorrhage (ICH) was observed in patients with a previous stroke; thus, all patients with a previous stroke were discontinued from the study. The prescribing information presents data from both the original cohort and the indicated population (post-MI and PAD). The protocol-defined primary endpoint was the composite of CV death, MI, stroke, or urgent coronary revascularization (UCR) and the major secondary endpoint was the composite of CV death, MI, or stroke. During the trial, prior to data lock or unblinding, the Steering Committee reordered the hierarchy of the efficacy endpoints based on another completed trial's results. The prescribing information considers the primary outcome measure to be the composite of CV death, MI, stroke, or UCR.

In TRA 2P – TIMI, patients who had evidence or a history of atherosclerosis involving the coronary, cerebral, or peripheral vascular systems were randomized to receive daily treatment with vorapaxar (n=13,225) or placebo (n=13,224) in addition to standard of care.[229,230] Standard-of-care included antiplatelet therapy with aspirin and/or clopidogrel, statins, beta-blockers, and angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). The study's primary endpoint was the composite of CV death, MI, stroke, and UCR. The composite of CV death, MI, and stroke was assessed as key secondary endpoint. The qualifying diagnosis was prior-MI in 67.3% and 67.2% of vorapaxar and placebo patients respectively, ischemic stroke in 18.4% and 18.5%, respectively of vorapaxar and placebo patients, and PAD in 14.3% in both groups. The median follow-up was 2.5 years (up to 4 years). In the original cohort (including those with a history of stroke), the findings in all randomized patients for the primary efficacy composite endpoint showed a 3-year Kaplan-Meier (K-M) event rate of 11.2% in the vorapaxar group compared to 12.4% in the placebo group (HR, 0.88; 95% CI, 0.82 to 0.95; p=0.001). The findings for the key secondary efficacy endpoint showed a 3 year K-M event rate of 9.3% in the vorapaxar group compared to 10.5% in placebo group (HR, 0.87; 95% CI, 0.8 to 0.94; p<0.001). The difference between vorapaxar and placebo in the secondary endpoint of death or MI was significant favoring vorapaxar (p=0.002). The difference between groups in individual components of the composite endpoints was significant for MI (p=0.001) but not for the endpoints of stroke, UCR, or death from any cause. In patients weighing less than 60 kg, vorapaxar did not favorably influence

outcomes. The primary safety endpoint of GUSTO moderate or severe bleeding occurred in 4.2% in the vorapaxar group versus 2.5% in the placebo group (HR, 1.66; p<0.001). Overall, ICH occurred in 102 patients (1%) in the vorapaxar group versus 53 patients (0.5%) in the placebo group (HR, 1.94; p<0.001). The difference between groups in fatal bleeding was not significant. Among those in the post-stroke cohort, the rate of ICH in the vorapaxar group was 2.4% versus 0.9% in the placebo group (p<0.001).

In the pre-defined sub-group analysis of patients with a qualifying diagnosis of MI, the CV death, MI, or stroke composite was reduced from 9.6% (K-M 3-year estimate) in the placebo group to 8.3% in the vorapaxar group (HR, 0.8; p<0.001). The composite of CV death, MI, stroke, or UCR was reduced from 11.8% in the placebo group to 10.6% in the vorapaxar group (HR 0.83; p<0.001). In this cohort, GUSTO moderate or severe bleeding occurred in 3.4% of vorapaxar patients (K-M 3-year estimate) versus 2.1% of placebo patients (HR, 1.61; p<0.001). The differences in rate of ICH and fatal bleeding were not significant.

In the pre-specified sub-group analysis of patients with a qualifying diagnosis of PAD, neither the CV death, MI, or stroke composite nor the CV death, MI, stroke or UCR composite were significant for vorapaxar versus placebo.[231] However, the secondary endpoint rates of hospitalization for acute limb ischemia occurred in 2.3% of vorapaxar patients versus 3.9% of placebo patients (HR, 0.58; p=0.006). Peripheral revascularization occurred in 18.4% versus 22.2% of vorapaxar and placebo patients, respectively (HR, 0.84; p=0.0017). The reduction was consistent for both urgent and elective revascularization. In this cohort, GUSTO moderate or severe bleeding occurred in 7.4% versus 4.5% of patients in the vorapaxar and placebo groups, respectively (HR, 1.62; p=0.001). When patients with a history of cerebrovascular disease were excluded, the rates of ICH were 0.7% for vorapaxar versus 0.4% for placebo (p=0.37).

META-ANALYSIS

Assessment of conventional and network meta-analyses for inclusion in this class review considers clinical importance and validity.

A meta-analysis of serious vascular events (MI, stroke, or vascular death) and major bleeds in 6 primary prevention trials and 16 secondary prevention trials compared long-term immediate release aspirin versus control.[232] In the primary prevention trials, aspirin allocation yielded a 12% proportional reduction in serious vascular events (0.51% aspirin versus 0.57% control per year, p=0.0001), due mainly to a reduction of about a fifth in non-fatal MI (0.18% versus 0.23% per year; p<0.0001). The net effect on stroke was not significant (0.2% versus 0.21% per year; p=0.4). Aspirin increased major GI and extracranial bleeds (0.1% versus 0.07% per year; p<0.0001). In the secondary prevention trials, aspirin yielded a greater absolute reduction in serious vascular events (6.7% versus 8.2% per year; p<0.0001), with a non-significant increase in hemorrhagic stroke but reductions of about one fifth in total stroke (2.08% versus 2.54% per year; p=0.002) and in coronary events (4.3% versus 5.3% per year; p<0.0001). In both primary and secondary prevention trials, the proportional reductions in the aggregate of all serious vascular events seemed similar for men and women. In a similar meta-analysis (12 trials; n=15,778), the authors evaluated pooled data comparing aspirin to control in recurrent stroke following ischemic stroke or TIA.[233] The authors found that aspirin reduced 6 week early recurrent ischemic stroke by nearly 60% (HR, 0.42; 95% CI, 0.32 to 0.55; p<0.0001). It also reduced fatal ischemic stroke by approximately 70% (HR, 0.29; 95% CI, 0.2 to 0.42; p<0.0001). Data for aspirin also was

compared to aspirin plus dipyridamole (8 trials; n=11,937). No difference was found with the addition of dipyridamole within 12 weeks (OR, 0.9; 95% CI, 0.65 to 1.25; p=0.53), but a difference favoring dipyridamole was found thereafter (OR, 0.76; 95% CI, 0.63 to 0.92; p=0.005).

A meta-analysis of 10 randomized controlled trials comparing aspirin plus clopidogrel with aspirin monotherapy in patients with transient ischemic attack (TIA) or ischemic stroke (IS) was conducted to determine the optimal duration of therapy to achieve safety and efficacy.[234] The analysis included a total of 15,434 patients who had received either short-term (1 month), intermediate-term (3 months), or long-term (> 3 months) course of treatment. For the primary efficacy outcome measure, aspirin plus clopidogrel therapy significantly reduced the risk of recurrent IS at both short-term (6.4% versus 10%; risk ratio [RR], 0.53; 95% CI, 0.37 to 0.78) and intermediate-term (4.8% versus 6.7%; RR, 0.72; 95% CI, 0.58 to 0.9) durations compared with aspirin monotherapy. Furthermore, there was no significant difference between both the groups at long-term duration (6.3% versus 7.7%; RR, 0.81; 95% CI, 0.63 to 1.04). For the primary safety outcome, short-term aspirin plus clopidogrel therapy was comparable to aspirin monotherapy (0.4% versus 0.2%; RR, 1.82; 95% CI, 0.91 to 3.62). Conversely, both intermediate-term (1.1% versus 0.4%; RR, 2.58; 95% CI, 1.19 to 5.6) and long-term (6.6% versus 3.4%; RR: 1.87; 95% CI, 1.36 to 2.56) durations significantly increased the risk of major bleeding.

Dipyridamole has no clear evidence of substantial benefit on vascular death compared to controls based on a systematic review evaluating the role of dipyridamole for preventing stroke and other vascular events in patients with vascular disease.[235] A total of 29 trials with 23,019 participants were included. Compared to the control group, dipyridamole had no effect on vascular death (relative risk [RR], 0.99; 95% CI, 0.87 to 1.12). The dose of dipyridamole did not influence the outcome nor did the type of vascular disease at presentation. For the risk of vascular events, dipyridamole did significantly reduce the risk only for patients presenting with cerebral ischemia. There was no evidence that dipyridamole monotherapy was more efficacious than aspirin.

The combination of aspirin with dipyridamole ER has shown to be beneficial in the Second European Stroke Prevention Study (ESPS-2) in patients with cerebral ischemia.[236] A meta-analysis pooling data from 5 trials with a total of 11,459 patients with a history of TIA or ischemic stroke found that aspirin/dipyridamole reduced the composite of nonfatal stroke, nonfatal MI, and vascular death as compared with aspirin alone (OR, 0.84; 95% CI, 0.72 to 0.97), dipyridamole alone (OR, 0.76; 95% CI, 0.64 to 0.9), or control (OR, 0.66; 95% CI, 0.57 to 0.75).[237] It should be noted that 57% of the data were from the ESPS-2 trial.

A meta-analysis of 6 randomized trials with 7,648 patients showed a significant reduction in the overall stroke risk ratio with aspirin plus dipyridamole compared with aspirin alone (RR, 0.77; 95% CI, 0.67 to 0.89) and composite outcome of stroke, MI, or vascular death with relative risk 0.85 (95% CI, 0.76 to 0.94).[238] Studies using immediate-release dipyridamole showed a non-statistically significant trend in favor of the combination for stroke alone with relative risk 0.83 (95% CI, 0.59 to 1.15) and for the composite outcome with relative risk 0.95 (95% CI, 0.75 to 1.19). Studies using predominantly extended-release dipyridamole showed a statistically significant difference in favor of the combination for stroke alone with relative risk 0.76 (95% CI, 0.65 to 0.89) and for the composite outcome with relative risk 0.82 (95% CI, 0.73 to 0.92). Approximately 80% of the patients in this meta-analysis were from the ESPS-2 and ESPIRIT trials.

A meta-analysis of 3 randomized trials, PCI-CURE, CREDO, and PCI-CLARITY was performed to evaluate the efficacy and safety of clopidogrel (Plavix) pre-treatment before PCI intervention with and without

glycoprotein IIb/IIIa inhibitor (GPI) use.[239] A total of 6,325 patients were included; 32.4% of them received a GPI. There was a consistent benefit of clopidogrel pretreatment in reducing the incidence of CV death, MI, or stroke after PCI both in patients who did not receive a GPI (OR, 0.72; 95% CI, 0.53 to 0.98; p=0.03) and in those who did (OR, 0.69; 95% CI, 0.47 to 1; p=0.05). Clopidogrel pretreatment was not associated with a significant increase in bleeding.

In a network meta-analysis (30 trials; n=34,563) comparing the safety and efficacy of prasugrel, ticagrelor, and both high- and standard-dose clopidogrel in patients undergoing PCI, prasugrel was found to be the most effective for definite or probable stent thrombosis (statistically significant odds ratio versus ticagrelor and standard-dose clopidogrel), followed by high-dose clopidogrel and ticagrelor (both statistically superior to clopidogrel standard dose).[240] Standard dose clopidogrel was found to be the least effective. MI was least likely to be prevented by standard-dose clopidogrel (OR > 1 versus other agents) with no statistically significant difference between the other agents. No statistically significant difference was found in prevention of CV death. On the other hand, high dose clopidogrel outperformed prasugrel in bleeding complications, but no statistically significant difference was found in TIMI major bleeding. As it is a network meta-analysis, results should be interpreted cautiously. A meta-analysis (12 trials; n=3,956) evaluating the benefit of a prasugrel switch in patients undergoing PCI, found that a switch did not increase major bleeding compared to standard therapy (OR, 0.7; 95% CI, 0.39 to 1.25; p=0.23).[241] However, a difference in mortality was not found.

A meta-analysis of 4 randomized trials (n=31,470; DISPERSE-2, TRILOGY ACS, PLATO [NSTE-ACS], and TRITON-TIMI 38 [NSTE-ACS]) compared the efficacy and safety of prasugrel and ticagrelor to clopidogrel in patients non-ST-elevated ACS.[242] The primary outcome was a composite endpoint of major CV events (CV death, MI, or stroke). Secondary outcomes were components of major CV events, all-cause mortality, and TIMI major and minor bleeding. The newer agents, prasugrel and ticagrelor, decreased major CV events (RR, 0.87; 95% CI, 0.8 to 0.95) and MI (RR, 0.85; 95% CI, 0.75 to 0.96) compared to clopidogrel, but no statistically significant difference was found in CV death (RR, 0.89; 95% CI, 0.71 to 1.01). However, there was a significant increase in TIMI major and minor bleeding with the newer agents compared to clopidogrel (RR, 1.2; 95% CI, 1.02 to 1.42). Due to paucity of data, stent thrombosis was not evaluated. The authors concluded that the newer agents, prasugrel and ticagrelor, are more effective than clopidogrel at decreasing the composite of major CV events and MI but have a higher risk of bleeding associated with their use.

Another meta-analysis of 9 randomized trials (n=25,214; TRITON-TIMI 38, TRILOGY ACS, PRASFIT-ACS, JUMBO-TIMI26, PRINCIPLE-TIMI 44, OPTIMUS-3, TAILOR, ACAPULCO, and Alexopoulos, et al.), was performed to evaluate if the higher bleeding risk associated with prasugrel compared to clopidogrel would be outweighed by its improvement in decreased major CV events.[243] Overall, the risks of major CV events outweighed the risks of major (OR, 7.48; 95% CI, 3.75 to 14.94; p<0.0001) and minor (OR, 3.77; 95% CI, 1.73 to 8.22; p=0.009) bleeding using a random-effects model, suggesting an advantage of prasugrel over clopidogrel despite an increased risk of bleed. Results with fixed-effects were comparable. Limitations of this meta-analysis include that not all trials included were conducted in the US and heterogeneity of the studies.

In 2020, a Bayesian network meta-analysis including 26 randomized controlled trials (n = 51,465) was conducted to determine the efficacy and safety of antiplatelet therapies (mono versus dual versus combination with anticoagulants) in patients with symptomatic PAD.[244] The analysis found that clopidogrel (HR, 0.78; 95% CI, 0.65 to 0.93) significantly reduced major adverse cardiovascular event

(MACE) risk compared with aspirin. No significant difference was seen for dual antiplatelet therapy with clopidogrel plus aspirin, though a trend toward reduced risk of amputation over aspirin alone (risk ratio 0.68; 95% CI, 0.43 to 1.04) was shown. Clopidogrel demonstrated a comparable overall bleeding risk as aspirin; however, dual antiplatelet therapy with clopidogrel plus aspirin significantly increased the risk for bleeding. Vorapaxar significantly decreased limb ischemia as well as revascularization over placebo, and demonstrated a significantly lower risk for all-cause mortality compared to aspirin. The authors concluded that the review supports clopidogrel as a favored PAD treatment option based on its significant reduction in risk of MACE versus aspiring without an increased risk for bleeding, while acknowledging major limitations of the analysis, including that 93% of participants had recently undergone peripheral revascularization.

SUMMARY

Platelet aggregation inhibitors are used to prevent and treat a variety of thrombotic events including myocardial infarction, stroke and transient ischemic attack, and peripheral arterial disease. Various guidelines have specific recommendations for platelet aggregation inhibitor use.

Clopidogrel (Plavix) has been established for use in the management of a variety of cardiovascular and cerebrovascular conditions associated with thrombotic events. The effectiveness of clopidogrel is dependent on its conversion to its active metabolite, largely by CYP2C19. However, recent evidence indicates that patients with genetically reduced CYP2C19 function have lower systemic exposure to the active metabolite of clopidogrel, diminished antiplatelet responses, and generally exhibit higher cardiovascular event rates following myocardial infarction than patients with normal CYP2C19 function. In addition, concomitant use of proton-pump inhibitors (particularly proton-pump inhibitors extensively inhibited by CYP2C19) with clopidogrel may increase cardiovascular events. Concomitant use of clopidogrel with omeprazole or esomeprazole should be avoided.

Prasugrel (Effient) is approved to reduce cardiovascular events in acute coronary syndrome patients undergoing percutaneous coronary intervention, and it is reported to be more effective than clopidogrel in preventing myocardial infarction and stent thrombosis in this population. However, these gains are tempered by a significant increase in bleeding events. Prasugrel should not be used in patients with a prior history of stroke or transient ischemic attack.

Ticagrelor (Brilinta) differs from the thienopyridines (clopidogrel and prasugrel) as it binds reversibly instead of irreversibly with $P2Y_{12}$ platelet receptor, and it has a more rapid onset of action than clopidogrel. Ticagrelor is indicated for the reduction of thrombotic cardiovascular events in patients with acute coronary syndrome (unstable angina, non-ST-elevation myocardial infarction [NSTEMI], or ST-elevation myocardial infarction [STEMI]). Ticagrelor has shown to significantly reduce the rate of death from cardiovascular causes, myocardial infarction, or stroke compared with clopidogrel. However, this benefit did not show in a subgroup analysis of patients enrolled in North America. Although ticagrelor does not increase the risk of major bleeding overall, it does increase major non-coronary artery bypass graft bleeding. When given with ticagrelor, the daily maintenance doses of aspirin should not exceed 100 mg daily since higher doses will decrease ticagrelor effectiveness. In May 2020, ticagrelor received approval for reducing the risk of a first MI or stroke in patients with CAD at high risk for such events based on data from the THEMIS study demonstrating a reduction in the composite of CV death, MI, or stroke with ticagrelor plus aspirin compared to placebo plus aspirin (7.7% versus 8.5%, respectively HR, 0.9; 95% CI, 0.81 to 0.99; p=0.04). However, the ticagrelor-treated patients

also demonstrated a higher incidence of major bleed than with placebo (2.2% versus 1%, respectively; HR, 2.32; 95% CI, 1.82 to 2.94; p<0.001). In November 2020, ticagrelor received approval for reducing the risk of stroke in patients with acute ischemic stroke (National Institutes of Health [NIH] Stroke Scale score ≤ 5) or high-risk transient ischemic attack (TIA) based on findings from the THALES study which demonstrated a statistically significant reduction in the primary composite endpoint of stroke or death within 30 days with ticagrelor plus aspirin compared to aspirin alone (5.5% versus 6.6%, respectively; HR, 0.83; 95% CI, 0.71 to 0.96; p=0.02). However, severe bleeding was higher in the ticagrelor plus aspirin group (0.5%) compared to the aspirin only study arm (0.1%; p=0.001). Both ticagrelor and prasugrel result in more intense platelet inhibition compared to clopidogrel. Unlike clopidogrel, prasugrel and ticagrelor are not expected to interact with proton-pump inhibitors.

Current guidelines from the American College of Chest Physicians and the American College of Cardiology/American Heart Association include prasugrel and ticagrelor, in addition to clopidogrel, as options for dual antiplatelet therapy with aspirin for the treatment of patients with unstable angina/NSTEMI/non-ST-segment elevation-acute coronary syndrome. Prasugrel and ticagrelor were also added to the American College of Cardiology/American Heart Association 2013 guidelines for STEMI.

Vorapaxar (Zontivity), the first protease-activated receptor-1 (PAR-1) antagonist, is an option to reduce thrombotic cardiovascular events as add-on therapy to standard-of-care treatment (aspirin and/or clopidogrel) to further reduce the risk of cardiovascular death, myocardial infarction, stroke, and urgent cardiovascular revascularization in patients with a prior myocardial infarction or with peripheral arterial disease. Although the place in therapy for vorapaxar has not yet been clearly established or fully addressed in clinical practice guidelines, the demonstrated benefit appears to be strongest in the stable post-MI population without risk factors for bleeding. Caution should be used when choosing vorapaxar therapy due to an increase in moderate and severe bleeding in the pivotal clinical trial.

Immediate-release aspirin is available over the counter and used for secondary prevention of myocardial infarction, stable and unstable angina, including coronary artery disease, arterial thromboembolism prophylaxis for patients with prosthetic heart valves in combination with warfarin, secondary prevention of stroke/transient ischemic attack, and acute treatment of stroke in patients not eligible for thrombolysis. More recently, Yosprala, a delayed-release combination product containing aspirin and omeprazole, a proton pump inhibitor, was approved for patients who require aspirin therapy who are also at risk for developing gastric ulcers.

Aspirin/dipyridamole is indicated for risk reduction of stroke in patients who have had transient ischemia of the brain or completed ischemic thrombotic stroke due to thrombosis.

The American Heart Association/American Stroke Association recommends aspirin monotherapy or aspirin/dipyridamole ER monotherapy for the secondary stroke prevention. Clopidogrel monotherapy is a reasonable option for secondary prevention of stroke in place of aspirin or aspirin/dipyridamole ER, especially for patients allergic to aspirin. The American College of Chest Physicians states all 3 are acceptable options for long-term secondary stroke prevention.

Dipyridamole is indicated as adjunctive therapy to coumarin anticoagulants in the prevention of postoperative thromboembolic complications of cardiac valve replacement.

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